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(71) Applicant *(for all designated States except US)*: **FIBROGEN, INC.** [US/US]; 225 Gateway Boulevard, South San Francisco, CA 94080 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **KLAUS, Stephen, J.** [US/US]; 1255 California Street, #702, San Francisco, CA 94109 (US). **LIN, Al, Y.** [US/US]; 7884 Pineville Circle, Castro Valley, CA 94552 (US). **NEFF, Thomas, B.** [US/US]; 190 Glenwood Avenue, Atherton, CA 94027 (US). **WANG, Qingjian** [US/US]; 2115 Everglades Place, Davis, CA 95616 (US). **GUENZLER-PUKALL, Volkmar** [DE/US]; 1408 Regent Drive, San Leandro, CA 94577 (US). **AREND, Michael, P.** [DE/US]; 36 East 40th Avenue, Apartment #E, San Mateo, CA 94403 (US). **FLIPPIN, Lee, A.** [US/US]; 17659 Skyline Boulevard, Woodside, CA 94062 (US). **MELEKHOV, Alex** [RU/US]; 2153 Vista Del Mar, San Mateo, CA 94404 (US).

(74) Agents: **PRICE, Leanne, C.** et al.; Intellectual Property Department, Fibrogen, Inc., 225 Gateway Boulevard, South San Francisco, CA 94080 (US).

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(54) Title: METHODS OF INCREASING ENDOGENOUS ERYTHROPOIETIN (EPO)

(57) Abstract: The present invention relates to methods for treating erythropoietin-associated conditions by increasing endogenous erythropoietin *in vitro* and *in vivo*. Methods for treating, pretreating or preconditioning, or preventing erythropoietin-associated conditions are also included. Compounds for use in these methods are provided, as are methods of identifying such compounds.

METHODS OF INCREASING ENDOGENOUS ERYTHROPOIETIN (EPO)

[0001] This application claims the benefit of U.S. Provisional Application Serial No. 60/349,659, filed on 16 January 2002; U.S. Provisional Application Serial No. 60/386,488, filed on 5 June 2002; U.S. Provisional Application Serial No. 60/337,082, filed on 6 December 2001; and U.S. Provisional Application Serial No. 60/359,683, filed on 25 February 2002; each of which is incorporated by reference herein in its entirety.

FIELD OF THE INVENTION

[0002] The present invention relates to methods for increasing endogenous erythropoietin, *ex vivo* and *in vivo*, and to compounds that can be used in the methods.

BACKGROUND OF THE INVENTION

[0003] Erythropoietin (EPO), a naturally occurring hormone, stimulates the production of red blood cells (erythrocytes), which carry oxygen throughout the body. EPO is normally secreted by the kidneys, and endogenous EPO is increased under conditions of reduced oxygen (hypoxia). All types of anemia are characterized by the blood's reduced capacity to carry oxygen, and thus are associated with similar signs and symptoms, including pallor of the skin and mucous membranes, weakness, dizziness, easy fatigability, and drowsiness, leading to a decrease in quality of life. Subjects with severe cases of anemia show difficulty in breathing and heart abnormalities. Anemia is typically associated with a condition in which the blood is deficient in red blood cells or in hemoglobin.

[0004] Common causes of anemia include deficiencies of iron, vitamin B_{12}, and folic acid. Anemia can also develop in association with chronic diseases, e.g., in inflammatory disorders, including disorders with consequent inflammatory suppression of marrow, etc. Anemia may be caused by loss of blood, for example, due to accidents, surgery, or gastrointestinal bleeding caused by medications such as aspirin and ibuprofen. Excessive blood loss can also be seen in women with heavy menstrual periods, and in people with stomach ulcers, duodenal ulcers, hemorrhoids, or cancer of the stomach or large intestine, etc.

[0005] Various conditions can cause the destruction of erythrocytes (hemolysis), thus leading to anemia. For example, allergic-type reactions to bacterial toxins and various chemical agents such as sulfonamides and benzene can cause hemolysis. Hemolytic anemia is often caused by chemical poisoning, parasites, infection, or sickle-cell anemia. In addition, there are unusual situations in which the body produces antibodies against its own erythrocytes, resulting in hemolysis. Any disease or injury to the bone marrow can cause

anemia, since that tissue is the site of erythropoiesis, i.e. erythrocyte synthesis. Irradiation, disease, or various chemical agents can also cause bone marrow destruction, producing aplastic anemia. Cancer patients undergoing chemotherapy often have aplastic anemia. Anemia is also associated with renal dysfunction, the severity of the anemia correlating highly with the extent of the dysfunction. Most patients with renal failure undergoing dialysis suffer from chronic anemia.

[0006] In addition to being produced in the kidney, erythropoietin is produced by astrocytes and neurons in the central nervous system (CNS), and EPO and EPO receptors are expressed at capillaries of the brain-periphery interface. Furthermore, systemically administered EPO crosses the blood-brain barrier and reduces neuronal cell loss in response to cerebral and spinal chord ischemia, mechanical trauma, epilepsy, excitotoxins, and neuroinflammation. (Sakanaka (1998) Proc Natl Acad Sci U S A 95:4635-4640; Celik et al. (2002) Proc Natl Acad Sci USA 99:2258-2263; Brines et al. (2000) Proc Natl Acad Sci USA 97:10526-10531; Calapai et al. (2000) Eur J Pharmacol 401:349-356; and Siren et al. (2001) Proc Natl Acad Sci USA 98:4044-404.)

[0007] In the late 1980s, Amgen introduced a genetically engineered EPO for the treatment of anemia in chronic renal failure patients. EPO is also administered to cancer patients undergoing radiation and/or chemotherapy, decreasing the need for blood transfusions. EPO is used to treat anemia associated with HIV infection or azidothymidine (AZT) therapy. Although the market for EPO therapy is increasing, future sales are adversely affected by the high cost of the product. In addition, recombinant EPO therapy requires intravenous administration of EPO one to three times per week for up to twelve weeks, a treatment regimen that limits self-administration and is inconvenient for the patient. Further, human serum EPO shows size heterogeneity due to extensive and varied glycosylation not reproduced in any recombinant human EPO.

[0008] Due to deficiencies in current production and use of recombinant EPO, there remains a need for methods and compounds effective in the treatment of erythropoietin-associated conditions such as anemia, including anemia associated with diabetes, ulcers, kidney failure, cancer, infection, dialysis, surgery, and chemotherapy. Specifically, there is a need in the art for methods and compounds that increase endogenous erythropoietin.

SUMMARY OF THE INVENTION

[0009] The present invention relates generally to methods for increasing endogenous erythropoietin. In one aspect, the present invention provides a method of increasing

endogenous erythropoietin (EPO) in a subject, the method comprising stabilizing the alpha subunit of hypoxia inducible factor (HIFα). In another aspect, the present invention provides a method of increasing endogenous EPO in a subject, the method comprising inhibiting hydroxylation of HIFα. In yet another aspect, a method of increasing endogenous EPO in a subject, the method comprising inhibiting 2-oxoglutarate dioxygenase enzyme activity, is provided. The present invention provides in a further aspect a method of increasing endogenous EPO levels in a subject, the method comprising inhibiting HIF prolyl hydroxylase enzyme activity.

[0010] The subject can be, in various embodiments, an animal, a mammal, a human, a cell, a tissue, an organ, etc.

[0011] In one aspect, the invention provides a method of increasing endogenous EPO, the method comprising stabilizing HIFα, wherein the stabilizing takes place *in vivo*. A method of increasing endogenous EPO, the method comprising stabilizing HIFα, wherein the ~~stabilizing takes place *in vitro*, is also contemplated.~~

[0012] In particular embodiments of the invention in which methods of stabilizing endogenous HIFα are contemplated, the HIFα is selected from the group consisting of HIF-1α, HIF-2α, HIF-3α, and any fragment thereof. In one embodiment, the HIFα is endogenous to the subject.

[0013] In methods of the invention relating to inhibition of 2-oxoglutarate dioxygenase enzyme activity, various embodiments are provided in which the 2-oxoglutarate dioxygenase enzyme is selected from the group consisting of EGLN1, EGLN2, EGLN3, procollagen prolyl 4-hydroxylase, procollagen prolyl 3-hydroxylase, procollagen lysyl hydroxylase, PHD4, FIH-1, and any subunit or fragment thereof. With respect to methods for increasing endogenous EPO which comprise inhibiting HIF prolyl hydroxylase enzyme activity, embodiments in which the HIF prolyl hydroxylase enzyme is selected from the group consisting of EGLN1, EGLN2, EGLN3, and any subunit or fragment thereof are contemplated.

[0014] A preferred method for increasing endogenous EPO according to the present invention comprises administering to the subject a compound that increases endogenous EPO. In one aspect, the compound stabilizes HIFα. In another aspect, the compound inhibits hydroxylation of HIFα. In a further aspect, the compound inhibits 2-oxoglutarate

dioxygenase enzyme activity. In a particular aspect, the compound inhibits HIF prolyl hydroxylase enzyme activity.

[0015] In certain embodiments, the present invention provides a method for increasing endogenous EPO in a subject, the method comprising administering to the subject a compound selected from the group consisting of heterocyclic carboxamides, phenanthrolines, hydroxamates, and physiologically active salts and prodrugs derived therefrom. In a particular embodiment, the compound is a heterocyclic carboxamide selected from the group consisting of pyridine carboxamides, quinoline carboxamides, isoquinoline carboxamides, cinnoline carboxamides, and beta-carboline carboxamides. In a preferred embodiment, the compound is delivered to the subject in the form of an oral formulation. In another preferred embodiment, the compound is delivered in a transdermal formulation.

[0016] Various methods for treating, preventing, or pretreating an EPO-associated disorder in a subject are provided. In one aspect, the present invention provides a method for treating, preventing, or pretreating an EPO-associated disorder, the method comprising increasing endogenous EPO. In another aspect, a method for treating, preventing, or pretreating an EPO-associated disorder in a subject, the method comprising stabilizing HIFα, is provided. In another method according to the present invention, a method of treating, preventing, or pretreating an EPO-associated disorder in a subject comprises inhibiting hydroxylation of HIFα. In yet another aspect, the invention provides a method of treating, preventing, or pretreating an EPO-associated disorder in a subject, the method comprising inhibiting 2-oxoglutarate dioxygenase enzyme activity. In a preferred aspect of the present invention, a method for treating, preventing, or pretreating an EPO-associated disorder in a subject, the method comprising inhibiting HIF prolyl hydroxylase enzyme activity, is contemplated.

[0017] The present invention specifically relates to methods for treating, preventing, or pretreating anemia in a subject. In one embodiment, the method comprises increasing endogenous EPO, including, in various embodiments, stabilizing HIFα, inhibiting 2-oxoglutarate dioxygenase enzyme activity, inhibiting HIF prolyl hydroxylase enzyme activity, etc.

[0018] In one aspect, the invention provides methods for treatment, prevention, and pretreatment/ preconditioning of anemia, wherein the anemia is associated with abnormal hemoglobin or erythrocytes. In a further aspect, the anemia is associated with a condition selected from the group consisting of diabetes, cancer, ulcers, kidney disease,

immunosuppressive disease, infection, and inflammation. In yet another aspect, the anemia is associated with a procedure or treatment selected from the group consisting of radiation therapy, chemotherapy, dialysis, and surgery. In another aspect, methods for treatment, prevention, and pretreatment/preconditioning of anemia, wherein the anemia is associated with blood loss, are provided. In various aspects, the blood less is associated with bleeding disorders, trauma, injury, surgery, etc. It is contemplated in specific embodiments that the anemia can be associated with defects in iron transport, processing, or utilization. Methods of pretreating/preconditioning, preventing, or treating anemia, the methods comprising increasing endogenous EPO, and further comprising administering to the subject a compound selected from the group consisting of, e.g., an iron supplement, vitamin B_{12}, folic acid, exogenous erythropoietin, and granulocyte-colony stimulating factor, etc., are also contemplated.

[0019] The present invention further relates to a method of treating, preventing, or pretreating a neurological disorder in a subject, the method comprising increasing endogenous EPO. In various aspects, the method comprises stabilizing HIFα, inhibiting 2-oxoglutarate dioxygenase enzyme activity, and inhibiting HIF prolyl hydroxylase enzyme activity. The invention contemplates in certain aspects that the neurological disorder is associated with a condition selected from the group consisting of stroke, trauma, epilepsy, and neurodegenerative disease.

[0020] In one embodiment, the present invention includes a method of enhancing oxygen consumption in a subject, the method comprising increasing endogenous EPO.

[0021] Methods for identifying compounds that increase endogenous EPO in a subject are also provided. In one embodiment, the invention contemplates a method of identifying a compound that increases endogenous EPO, the method comprising administering a compound to a subject; measuring EPO in the subject or in a sample from the subject; and comparing the EPO in the subject or in the sample to a standard, wherein an increase in the EPO in the subject or in the sample relative to the standard is indicative of a compound that increases endogenous EPO.

[0022] The methods of the invention increase endogenous erythropoietin *ex vivo*, e.g., in cell culture, or *in vivo*, e.g., in an animal. Preferably, the animal is a mammal, e.g., a cat or dog, and, more preferably, the animal is a human. In certain embodiments, the methods of the invention increase synthesis of endogenous erythropoietin in tissues including, but not limited to, renal, hepatic, hematopoietic, and/or neural tissues. In other embodiments, the

methods of the invention are used to prevent, pretreat, or treat erythropoietin-associated conditions including neurological disorders and anemia. Erythropoietin-associated conditions associated with anemia include, but are not limited to, polycystic kidney disease, chronic renal failure, diabetes, cancer, ulcers, and immunosuppressive conditions such as AIDS. In further embodiments, the methods of the invention are used to treat anemia associated with procedures or treatments including, but not limited to, radiation therapy, chemotherapy, kidney dialysis, or surgery. In specific embodiments, the methods of the invention are used to increase endogenous erythropoietin levels in an HIV-infected anemic subject being treated with zidovudine or other reverse transcriptase inhibitors. In other embodiments, the methods are used to increase endogenous erythropoietin levels in an anemic cancer patient receiving cyclic cisplatin- or non-cisplatin-containing chemotherapy. In further embodiments, the methods are used to increase endogenous erythropoietin levels in an anemic patient scheduled to undergo elective, noncardiac, nonvascular surgery, thereby reducing the need for allogenic blood transfusions or to facilitate banking of blood prior to surgery. In one specific embodiment, the method is used to increase endogenous erythropoietin levels in a subject prior to procedures such as, e.g., surgery requiring aortic clamping such as thoracoabdominal aortic surgery. In yet another embodiment, the method is used to increase endogenous erythropoietin produced by cells *in vitro*.

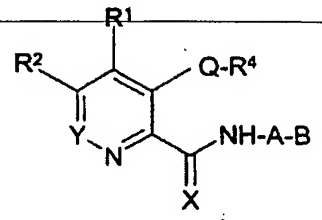
[0023] In one aspect, the invention provides compounds that increase endogenous erythropoietin plasma levels. In one embodiment, a therapeutically effective amount of the compound or a pharmaceutically acceptable salt thereof, alone or in combination with a pharmaceutically acceptable excipient, is administered to a subject having an erythropoietin-associated condition. In another aspect, a therapeutically effective amount of the compound or a pharmaceutically acceptable salt thereof, alone or in combination with a pharmaceutically acceptable excipient, is administered to a patient having anemia.

[0024] Preferred embodiments of the invention comprise methods using oral and transdermal delivery mechanisms. Such mechanisms could provide advantages over current therapies, e.g., increased ease of administration, self-administration by patient, reduced cost, fewer physician visits, and reduced risks due to infection and immunogenic complications, minimizing the adverse reactions some subjects develop in response to dosing with recombinant EPO. In one preferred embodiment, the present methods involve oral administration of a compound that increases endogenous erythropoietin levels. Thus, the present invention also provides an oral formulation comprising a compound of the invention. In another preferred embodiment, the present methods involve transdermal administration of a

compound that increases endogenous erythropoietin levels. Thus, the present invention also provides a transdermal patch or pad comprising a compound of the invention.

[0025] In another aspect, the invention provides compounds that increase endogenous erythropoietin produced by cells in culture and methods of using the compounds to produce erythropoietin using *in vitro* cell culture technologies. In one embodiment, the method comprises adding an effective amount of the compound or a pharmaceutically acceptable salt thereof to cells in culture under conditions suitable for production of erythropoietin, and collecting and purifying the erythropoietin produced thereby. Examples of cells that produce erythropoietin *in vitro* include hepatic cells such as Hep3B hepatocarcinoma cells.

[0026] In certain embodiments, compounds used in the methods of the invention are selected from a compound of the formula (I)



(I)

wherein

A is 1,2-arylidene, 1,3-arylidene, 1,4-arylidene; or (C_1-C_4)-alkylene, optionally substituted by one or two halogen, cyano, nitro, trifluoromethyl, (C_1-C_6)-alkyl, (C_1-C_6)-hydroxyalkyl, (C_1-C_6)-alkoxy, -O-$[CH_2]_x$-$C_fH_{(2f+1-g)}Hal_g$, (C_1-C_6)-fluoroalkoxy, (C_1-C_8)-fluoroalkenyloxy, (C_1-C_8)-fluoroalkynyloxy, -OCF_2Cl, -O-CF_2-CHFCl; (C_1-C_6)-alkylmercapto, (C_1-C_6)-alkylsulfinyl, (C_1-C_6)-alkylsulfonyl, (C_1-C_6)-alkylcarbonyl, (C_1-C_6)-alkoxycarbonyl, carbamoyl, N-(C_1-C_4)-alkylcarbamoyl, N,N-di-(C_1-C_4)-alkylcarbamoyl, (C_1-C_6)-alkylcarbonyloxy, (C_3-C_8)-cycloalkyl, phenyl, benzyl, phenoxy, benzyloxy, anilino, N-methylanilino, phenylmercapto, phenylsulfonyl, phenylsulfinyl, sulfamoyl, N-(C_1-C_4)-alkylsulfamoyl, N,N-di-(C_1-C_4)-alkylsulfamoyl; or by a substituted (C_6-C_{12})-aryloxy, (C_7-C_{11})-aralkyloxy, (C_6-C_{12})-aryl, (C_7-C_{11})-aralkyl radical, which carries in the aryl moiety one to five identical or different substituents selected from halogen, cyano, nitro, trifluoromethyl, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, -O-$[CH_2]_x$-$C_fH_{(2f+1-g)}Hal_g$, -OCF_2Cl, -O-CF_2-CHFCl, (C_1-C_6)-alkylmercapto, (C_1-C_6)-alkylsulfinyl, (C_1-C_6)-alkylsulfonyl, (C_1-C_6)-alkylcarbonyl, (C_1-C_6)-alkoxycarbonyl, carbamoyl, N-(C_1-C_4)-alkylcarbamoyl, N,N-di-(C_1-C_4)-alkylcarbamoyl, (C_1-C_6)-alkylcarbonyloxy, (C_3-C_8)-cycloalkyl, sulfamoyl, N-(C_1-C_4)-alkylsulfamoyl, N,N-di-(C_1-

C_4)-alkylsulfamoyl; or wherein A is $-CR^5R^6$ and R^5 and R^6 are each independently selected from hydrogen, (C_1-C_6)-alkyl, (C_3-C_7)-cycloalkyl, aryl, or a substituent of the α-carbon atom of an α-amino acid, wherein the amino acid is a natural L-amino acid or its D-isomer.

B is $-CO_2H$, $-NH_2$, $-NHSO_2CF_3$, tetrazolyl, imidazolyl, 3-hydroxyisoxazolyl, -CONHCOR'", -CONHSOR'", $CONHSO_2R'''$, where R'" is aryl, heteroaryl, (C_3-C_7)-cycloalkyl, or (C_1-C_4)-alkyl, optionally monosubstituted by (C_6-C_{12})-aryl, heteroaryl, OH, SH, (C_1-C_4)-alkyl, (C_1-C_4)-alkoxy, (C_1-C_4)-thioalkyl, (C_1-C_4)-sulfinyl, (C_1-C_4)-sulfonyl, CF_3, Cl, Br, F, I, NO2, -COOH, (C_2-C_5)-alkoxycarbonyl, NH_2, mono-(C_1-C_4-alkyl)-amino, di-(C_1-C_4-alkyl)-amino, or (C_1-C_4)-perfluoroalkyl; or wherein B is a CO_2-G carboxyl radical, where G is a radical of an alcohol G-OH in which G is selected from (C_1-C_{20})-alkyl radical, (C_3-C_8) cycloalkyl radical, (C_2-C_{20})-alkenyl radical, (C_3-C_8)-cycloalkenyl radical, retinyl radical, (C_2-C_{20})-alkynyl radical, (C_4-C_{20})-alkenynyl radical, where the alkenyl, cycloalkenyl, alkynyl, and alkenynyl radicals contain one or more multiple bonds; (C_6-C_{16})-carbocyclic aryl radical, (C_7-C_{16})-carbocyclic aralkyl radical, heteroaryl radical, or heteroaralkyl radical, wherein a heteroaryl radical or heteroaryl moiety of a heteroaralkyl radical contains 5 or 6 ring atoms; and wherein radicals defined for G are substituted by one or more hydroxyl, halogen, cyano, trifluoromethyl, nitro, carboxyl, (C_1-C_{12})-alkyl, (C_3-C_8)-cycloalkyl, (C_5-C_8)-cycloalkenyl, (C_6-C_{12})-aryl, (C_7-C_{16})-aralkyl, (C_2-C_{12})-alkenyl, (C_2-C_{12})-alkynyl, (C_1-C_{12})-alkoxy, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkyl, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxy, (C_6-C_{12})-aryloxy, (C_7-C_{16})-aralkyloxy, (C_1-C_8)-hydroxyalkyl, $-O-[CH_2]_x-C_pH_{(2p+1-g)}-F_g$, $-OCF_2Cl$, $-OCF_2-CHFCl$, (C_1-C_{12})-alkylcarbonyl, (C_3-C_8)-cycloalkylcarbonyl, (C_6-C_{12})-arylcarbonyl, (C_7-C_{16})-aralkylcarbonyl, cinnamoyl, (C_2-C_{12})-alkenylcarbonyl, (C_2-C_{12})-alkynylcarbonyl, (C_1-C_{12})-alkoxycarbonyl, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxycarbonyl, (C_6-C_{12})-aryloxycarbonyl, (C_7-C_{16})-aralkoxycarbonyl, (C_3-C_8)-cycloalkoxycarbonyl, (C_2-C_{12})-alkenyloxycarbonyl, (C_2-C_{12})-alkynyloxycarbonyl, acyloxy, (C_1-C_{12})-alkoxycarbonyloxy, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxycarbonyloxy, (C_6-C_{12})-aryloxycarbonyloxy, (C_7-C_{16}) aralkyloxycarbonyloxy, (C_3-C_8)-cycloalkoxycarbonyloxy, (C_2-C_{12})-alkenyloxycarbonyloxy, (C_2-C_{12})-alkynyloxycarbonyloxy, carbamoyl, N-(C_1-C_{12})-alkylcarbamoyl, N.N-di(C_1-C_{12})-alkylcarbamoyl, N-(C_3-C_8)-cycloalkyl-carbamoyl, N-(C_6-C_{16})-arylcarbamoyl, N-(C_7-C_{16})-aralkylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_6-C_{16})-arylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_7-C_{16})-aralkylcarbamoyl, N-((C_1-C_{10})-alkoxy-(C_1-C_{10})-alkyl)-carbamoyl, N-((C_6-C_{12})-aryloxy-(C_1-C_{10})alkyl)-carbamoyl, N-((C_7-C_{16})-aralkyloxy-(C_1-C_{10})-alkyl)-carbamoyl, N-(C_1-C_{10})-alkyl-N-((C_1-C_{10})-alkoxy-(C_1-C_{10})-alkyl)-carbamoyl, N-(C_1-C_{10})-alkyl-N-((C_6-C_{16})-aryloxy-(C_1-C_{10})-alkyl)-carbamoyl, N-(C_1-C_{10})-alkyl-N-((C_7-C_{16})-aralkyloxy-(C_1-C_{10})-alkyl)-carbamoyl, carbamoyloxy, N-(C_1-C_{12})-alkylcarbamoyloxy, N.N-di-(C_1-C_{12})-alkylcarbamoyloxy, N-(C_3-C_8)-cycloalkylcarbamoyloxy, N-(C_6-C_{12})-arylcarbamoyloxy, N-(C_7-C_{16})-aralkylcarbamoyloxy, N-(C_1-C_{10})-alkyl-N-(C_6-

C_{12})-arylcarbamoyloxy, N(C_1-C_{10})-alkyl-N-(C_7-C_{16})-aralkylcarbamoyloxy, N-((C_1-C_{10})-alkyl)-carbamoyloxy, N-((C_6-C_{12})-aryloxy-(C_1-C_{10})-alkyl)-carbamoyloxy, N-((C_7-C_{16})-aralkyloxy-(C_1-C_{10})-alkyl)-carbamoyloxy, N-(C_1-C_{10})-alkyl-N-((C_1-C_{10})-alkoxy-(C_1-C_{10})-alkyl)-carbamoyloxy, N-(C_1-C_{10})-alkyl-N-((C_6-C_{12})-aryloxy-(C_1-C_{10})-alkyl)-carbamoyloxy, N-(C_1-C_{10})-alkyl-N-((C_7-C_{16})-aralkyloxy-(C_1-C_{10})-alkyl)-carbamoyloxy, amino, (C_1-C_{12})-alkylamino, di-(C_1-C_{12})-alkylamino, (C_3-C_8)-cycloalkylamino, (C_2-C_{12})-alkenylamino, (C_2-C_{12})-alkynylamino, N-(C_6-C_{12})-arylamino, N-(C-C_{11})-aralkylamino, N-alkyl-aralkylamino, N-alkyl-arylamino, (C_1-C_{12})-alkoxyamino, (C_1-C_{12})-alkoxy-N-(C_1-C_{10})-alkylamino, (C_1-C_{12})-alkylcarbonylamino, (C_3-C_8)-cycloalkylcarbonylamino, (C_6-C_{12}) arylcarbonylamino, (C_7-C_{16})-aralkylcarbonylamino, (C_1-C_{12})-alkylcarbonyl-N-(C_1-C_{10})-alkylamino, (C_3-C_8)-cycloalkylcarbonyl-N-(C_1-C_{10})-alkylamino, (C_6-C_{12})-arylcarbonyl-N-(C_1-C_{10})alkylamino, (C_7-C_{11})-aralkylcarbonyl-N-(C_1-C_{10})-alkylamino, (C_1-C_{12})-alkylcarbonylamino-(C_1-C_8)-alkyl, (C_3-C_8)-cycloalkylcarbonylamino-(C_1-C_8)alkyl, (C_6-C_{12})-arylcarbonylamino-(C_1-C_8)-alkyl, (C_7-C_{12})-aralkylcarbonylamino(C_1-C_8)-alkyl, amino-(C_1-C_{10})-alkyl, N-(C_1-C_{10}) alkylamino-(C_1-C_{10})-alkyl, N.N-di-(C_1-C_{10})-alkylamino-(C_1-C_{10})-alkyl, (C_3-C_8)cycloalkylamino-(C_1-C_{10})-alkyl, (C_1-C_{12})-alkylmercapto, (C_1-C_{12})-alkylsulfinyl, (C_1-C_{12})-alkylsulfonyl, (C_6-C_{16})-arylmercapto, (C_6-C_{16})-arylsulfinyl, (C_6-C_{12})-arylsulfonyl, (C_7-C_{16})-aralkylmercapto, (C_7-C_{16})-aralkylsulfinyl, (C_7-C_{16})-aralkylsulfonyl, sulfamoyl, N-(C_1-C_{10})-alkylsulfamoyl, N.N-di(C_1-C_{10})-alkylsulfamoyl, (C_3-C_8)-cycloalkylsulfamoyl, N-(C_6-C_{12})-alkylsulfamoyl, N-(C_7-C_{16})-aralkylsulfamoyl, N-(C_1-C_{10})-alkyl-N-(C_6-C_{12})-arylsulfamoyl, N-(C_1-C_{10})-alkyl-N-(C_7-C_{16})-aralkylsulfamoyl, (C_1-C_{10})-alkylsulfonamido, N-((C_1-C_{10})-alkyl)-(C_1-C_{10})-alkylsulfonamido, (C_7-C_{16})-aralkylsulfonamido, or N-((C_1-C_{10})-alkyl-(C_7-C_{16})-aralkylsulfonamido; wherein radicals which are aryl or contain an aryl moiety, may be substituted on the aryl by one to five identical or different hydroxyl, halogen, cyano, trifluoromethyl, nitro, carboxyl, (C_1-C_{12})-alkyl, (C_3-C_8)-cycloalkyl, (C_6-C_{12})-aryl, (C_7-C_{16})-aralkyl, (C_1-C_{12})-alkoxy, (C_1-C_{12})-alkoxy-(C_1-C_{12})alkyl, (C_1-C_{12})-alkoxy-(C_1 C_{12})alkoxy, (C_6-C_{12})-aryloxy, (C_7-C_{16})-aralkyloxy, (C_1-C_8)-hydroxyalkyl, (C_1-C_{12})-alkylcarbonyl, (C_3-C_8)-cycloalkyl-carbonyl, (C_6-C_{12})-arylcarbonyl, (C_7-C_{16}) aralkylcarbonyl, (C_1-C_{12})-alkoxycarbonyl, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxycarbonyl, (C_6-C_{12})-aryloxycarbonyl, (C_7-C_{16})-aralkoxycarbonyl, (C_3-C_8)-cycloalkoxycarbonyl, (C_2-C_{12})-alkenyloxycarbonyl, (C_2-C_{12})-alkynyloxycarbonyl, (C_1-C_{12})-alkylcarbonyloxy, (C_3-C_8)-cycloalkylcarbonyloxy, (C_6-C_{12})-arylcarbonyloxy, (C_7-C_{16})-aralkylcarbonyloxy, cinnamoyloxy, (C_2-C_{12})-alkenylcarbonyloxy, (C_2-C_{12})-alkynylcarbonyloxy, (C_1-C_{12})-alkoxycarbonyloxy, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxycarbonyloxy, (C_6-C_{12})-aryloxycarbonyloxy, (C_7-C_{16})-aralkyloxycarbonyloxy, (C_3-C_8)-cycloalkoxycarbonyloxy, (C_2-C_{12})-alkenyloxycarbonyloxy, (C_2-C_{12})-alkynyloxycarbonyloxy, carbamoyl, N-(C_1-C_{12})-alkylcarbamoyl, N.N-di-(C_1-C_{12})-alkylcarbamoyl, N-(C_3-C_8)-cycloalkylcarbamoyl, N-(C_6-C_{12})-arylcarbamoyl, N-(C_7-C_{16})-aralkylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_6-C_{12})-

arylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_7-C_{16})-aralkylcarbamoyl, N-((C_1-C_{10})-alkoxy-(C_1-C_{10})-alkyl)-carbamoyl, N-((C_6-C_{12})-aryloxy-(C_1-C_{10})-alkyl)-carbamoyl, N-((C_7-C_{16})-aralkyloxy-(C_1-C_{10})-alkyl)-carbamoyl, N-(C_1-C_{10})-alkyl-N-((C_1-C_{10})-alkoxy-(C_1-C_{10})-alkyl)-carbamoyl, N-(C_1-C_{10})-alkyl-N-((C_6-C_{12})-aryloxy-(C_1-C_{10})-alkyl)-carbamoyl, N-(C_1-C_{10})-alkyl-N-((C_7-C_{16})-aralkyloxy-(C_1-C_{10})-alkyl)-carbamoyl, carbamoyloxy, N-(C_1-C_{12})-alkylcarbamoyloxy, N.N-di-(C_1-C_{12})-alkylcarbamoyloxy, N-(C_3-C_8)-cycloalkylcarbamoyloxy, N-(C_6-C_{12})-arylcarbamoyloxy, N-(C_7-C_{16})-aralkylcarbamoyloxy, N-(C_1-C_{10})-alkyl-N-(C_6-C_{12})-arylcarbamoyloxy, N(C_1-C_{10})-alkyl-N-(C_7-C_{16})-aralkylcarbamoyloxy, N-((C_1-C_{10})-alkyl)-carbamoyloxy, N-((C_6-C_{12})-aryloxy-(C_1-C_{10})-alkyl)-carbamoyloxy, N-((C_7-C_{16})-aralkyloxy-(C_1-C_{10})-alkyl)-carbamoyloxy, N-(C_1-C_{10})-alkyl-N-((C_1-C_{10})-alkoxy-(C_1-C_{10})-alkyl)-carbamoyloxy, N-(C_1-C_{10})-alkyl-N-((C_6-C_{12})-aryloxy-(C_1-C_{10})-alkyl)-carbamoyloxy, N-(C_1-C_{10})-alkyl-N-((C_7-C_{16})-aralkyloxy-(C_1-C_{10})-alkyl)-carbamoyloxy, amino, (C_1-C_{12})-alkylamino, di-(C_1-C_{12})-alkylamino, (C_3-C_8)-cycloalkylamino, (C_3-C_{12})-alkenylamino, (C_3-C_{12})-alkynylamino, N-(C_6-C_{12})-arylamino, N-(C_7-C_{11})-aralkylamino, N-alkylaralkylamino, N-alkyl-arylamino, (C_1-C_{12})-alkoxyamino, (C_1-C_{12})-alkoxy-N-(C_1-C_{10})-alkylamino, (C_1-C_{12})-alkylcarbonylamino, (C_3-C_8)-cycloalkylcarbonylamino, (C_6-C_{12})-arylcarbonylamino, (C_7-C_{16})-alkylcarbonylamino, (C_1-C_{12})-alkylcarbonyl-N-(C_1-C_{10})-alkylamino, (C_3-C_8)-cycloalkylcarbonyl-N-(C_1-C_{10})-alkylamino, (C_6-C_{12})-arylcarbonyl-N-(C_1-C_{10})-alkylamino, (C_7-C_{11})-aralkylcarbonyl-N-(C_1-C_{10})-alkylamino, (C_1-C_{12})-alkylcarbonylamino-(C_1-C_8)-alkyl, (C_3-C_8)-cycloalkylcarbonylamino-(C_1-C_8)-alkyl, (C_6-C_{12})-arylcarbonylamino-(C_1-C_8)-alkyl, (C_7-C_{16})-aralkylcarbonylamino-(C_1-C_8)-alkyl, amino-(C_1-C_{10})-alkyl, N-(C_1-C_{10})-alkylamino-(C_1-C_{10})alkyl, N.N-di-(C_1-C_{10})-alkylamino-(C_1-C_{10})-alkyl, (C_3-C_8)-cycloalkylamino-(C_1-C_{10})-alkyl, (C_1-C_{12})-alkylmercapto, (C_1-C_{12})-alkylsulfinyl, (C_1-C_{12})-alkylsulfonyl, (C_6-C_{12})-arylmercapto, (C_6-C_{12})-arylsulfinyl, (C_6-C_{12})-arylsulfonyl, (C_7-C_{16})-aralkylmercapto, (C_7-C_{16})-aralkylsulfinyl, or (C_7-C_{16})-aralkylsulfonyl;

X is O or S;

Q is O, S, NR', or a bond;

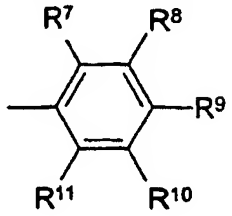
where, if Q is a bond, R^4 is halogen, nitrile, or trifluoromethyl;

or where, if Q is O, S, or NR', R^4 is hydrogen, (C_1-C_{10})-alkyl radical, (C_2-C_{10})-alkenyl radical, (C_2-C_{10})-alkynyl radical, wherein alkenyl or alkynyl radical contains one or two C-C multiple bonds; unsubstituted fluoroalkyl radical of the formula -$[CH_2]_x$-$C_fH_{(2f+1-g)}$-F_g, (C_1-C_8)-alkoxy-(C_1-C_6)-alkyl radical, (C_1-C_6)-alkoxy-(C_1-C_4)-alkoxy-(C_1-C_4)-alkyl radical, aryl radical, heteroaryl radical, (C_7-C_{11})-aralkyl radical, or a radical of the formula Z

$$-[CH_2]_v-[O]_w-[CH_2]_t-E \qquad (Z)$$

where

E is a heteroaryl radical, a (C_3-C_8)-cycloalkyl radical, or a phenyl radical of the formula F



(F)

v is 0-6,

w is 0 or 1,

t is 0-3, and

R^7, R^8, R^9, R^{10}, and R^{11} are identical or different and are hydrogen, halogen, cyano, nitro, trifluoromethyl, (C_1-C_6)-alkyl, (C_3-C_8)-cycloalkyl, (C_1-C_6)-alkoxy, -O-$[CH_2]_x$-$C_fH_{(2f+1-g)}$-F_g, -OCF_2-Cl, -O-CF_2-CHFCl, (C_1-C_6)-alkylmercapto, (C_1-C_6)-hydroxyalkyl, (C_1-C_6)-alkoxy-(C_1-C_6)-alkoxy, (C_1-C_6)-alkoxy-(C_1-C_6)-alkyl, (C_1-C_6)-alkylsulfinyl, (C_1-C_6)-alkylsulfonyl, (C_1-C_6)-alkylcarbonyl, (C_1-C_8)-alkoxycarbonyl, carbamoyl, N-(C_1-C_8)-alkylcarbamoyl, N,N-di-(C_1-C_8)-alkylcarbamoyl, or (C_7-C_{11})-aralkylcarbamoyl, optionally substituted by fluorine, chlorine, bromine, trifluoromethyl, (C_1-C_6)-alkoxy, N-(C_3-C_8)-cycloalkylcarbamoyl, N-(C_3-C_8)-cycloalkyl-(C_1-C_4)-alkylcarbamoyl, (C_1-C_6)-alkylcarbonyloxy, phenyl, benzyl, phenoxy, benzyloxy, NR^YR^Z wherein R^y and R^z are independently selected from hydrogen, (C_1-C_{12})-alkyl, (C_1-C_8)-alkoxy-(C_1-C_8)-alkyl, (C_7-C_{12})-aralkoxy-(C_1-C_8)-alkyl, (C_6-C_{12})-aryloxy-(C_1-C_8)-alkyl, (C_3-C_{10})-cycloalkyl, (C_3-C_{12})-alkenyl, (C_3-C_{12})-alkynyl, (C_6-C_{12})-aryl, (C_7-C_{11})-aralkyl, (C_1-C_{12})-alkoxy, (C_7-C_{12})aralkoxy, (C_1-C_{12})-alkylcarbonyl, (C_3-C_8)-cycloalkylcarbonyl, (C_6-C_{12}) arylcarbonyl, (C_7-C_{16})-aralkylcarbonyl; or further wherein R^y and R^z together are -[CH2]$_h$, in which a CH_2 group can be replaced by O, S, N-(C_1-C_4)-alkylcarbonylimino, or N-(C_1-C_4)-alkoxycarbonylimino; phenylmercapto, phenylsulfonyl, phenylsulfinyl, sulfamoyl, N-(C_1-C_8)-alkylsulfamoyl, or N, N-di-(C_1-C_8)-alkylsulfamoyl; or alternatively R^7 and R^8, R^8 and R^9, R^9 and R^{10}, or R^{10} and R^{11}, together are a chain selected from -$[CH_2]_n$- or -CH=CH-CH=CH-, where a CH_2 group of the chain is optionally replaced by O, S, SO, SO_2, or NR^Y; and n is 3, 4, or 5; and if E is a heteroaryl radical, said radical can carry 1-3 substituents selected from those defined for R^7-R^{11}, or if E is a cycloalkyl radical, the radical can carry one substituent selected from those defined for R^7-R^{11};

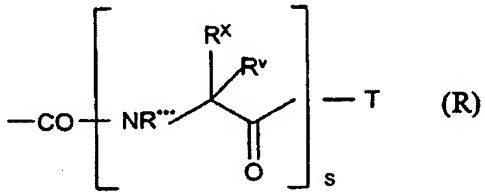
or where, if Q is NR', R^4 is alternatively R", where R' and R" are identical or different and are hydrogen, (C_6-C_{12})-aryl, (C_7-C_{11})-aralkyl, (C_1-C_8)-alkyl, (C_1-C_8)-alkoxy-(C_1-C_8)-alkyl, (C_7-C_{12})-aralkoxy-(C_1-C_8)-alkyl, (C_6-C_{12})-aryloxy-(C_1-C_8)-alkyl, (C_1-C_{10})-alkylcarbonyl,

optionally substituted (C_7-C_{16})-aralkylcarbonyl, or optionally substituted C_6-C_{12})-arylcarbonyl; or R' and R" together are -$[CH_2]_h$-, in which a CH_2 group can be replaced by O, S, N-acylimino, or N-(C_1-C_{10})-alkoxycarbonylimino, and h is 3 to 7.

Y is N or CR^3;

R^1, R^2 and R^3 are identical or different and are hydrogen, hydroxyl, halogen, cyano, trifluoromethyl, nitro, carboxyl, (C_1-C_{20})-alkyl, (C_3-C_8)-cycloalkyl, (C_3-C_8)cycloalkyl-(C_1-C_{12})-alkyl, (C_3-C_8)-cycloalkoxy, (C_3-C_8)-cycloalkyl-(C_1-C_{12})-alkoxy, (C_3-C_8)-cycloalkyloxy-(C_1-C_{12})-alkyl, (C_3-C_8)-cycloalkyloxy-(C_1-C_{12})-alkoxy, (C_3-C_8)-cycloalkyl-(C_1-C_8)-alkyl-(C_1-C_6)-alkoxy, (C_3-C_8)-cycloalkyl-(C_1-C_8)-alkoxy-(C_1-C_6)-alkyl, (C_3-C_8)-cycloalkyloxy-(C_1-C_8)-alkoxy-(C_1-C_6)-alkyl, (C_3-C_8)-cycloalkoxy-(C_1-C_8)-alkoxy-(C_1-C_8)-alkoxy, (C_6-C_{12})-aryl, (C_7-C_{16})-aralkyl, (C_7-C_{16})-aralkenyl, (C_7-C_{16})-aralkynyl, (C_2-C_{20})-alkenyl, (C_2-C_{20})-alkynyl, (C_1-C_{20})-alkoxy, (C_2-C_{20})-alkenyloxy, (C_2-C_{20})-alkynyloxy, retinyloxy, (C_1-C_{20})-alkoxy-(C_1-C_{12})-alkyl, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxy, (C_1-C_{12})-alkoxy-(C_1-C_8)-alkoxy-(C_1-C_8)-alkyl, (C_6-C_{12})-aryloxy, (C_7-C_{16})-aralkyloxy, (C_6-C_{12})-aryloxy-(C_1-C_6)-alkoxy, (C_7-C_{16})-aralkoxy-(C_1-C_6)-alkoxy, (C_1-C_{16})-hydroxyalkyl, (C_6-C_{16})-aryloxy-(C_1-C_8)-alkyl, (C_7-C_{16})-aralkoxy-(C_1-C_8)-alkyl, (C_6-C_{12})-aryloxy-(C_1-C_8)-alkoxy-(C_1-C_6)-alkyl, (C_7-C_{12})-aralkyloxy-(C_1-C_8)-alkoxy-(C_1-C_6)-alkyl, (C_2-C_{20})-alkenyloxy-(C_1-C_6)-alkyl, (C_2-C_{20})-alkynyloxy-(C_1-C_6)-alkyl, retinyloxy-(C_1-C_6)-alkyl, -O-$[CH_2]_xCfH_{(2f+1-g)}F_g$, -$OCF_2Cl$, -$OCF_2$-CHFCl, ($C_1$-$C_{20}$)-alkylcarbonyl, ($C_3$-$C_8$)-cycloalkylcarbonyl, ($C_6$-$C_{12}$)-arylcarbonyl, ($C_7$-$C_{16}$)-aralkylcarbonyl, cinnamoyl, (C_2-C_{20})-alkenylcarbonyl, (C_2-C_{20})-alkynylcarbonyl, (C_1-C_{20})-alkoxycarbonyl, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxycarbonyl, (C_6-C_{12})-aryloxycarbonyl, (C_7-C_{16})-aralkoxycarbonyl, (C_3-C_8)-cycloalkoxycarbonyl, (C_2-C_{20})-alkenyloxycarbonyl, retinyloxycarbonyl, (C_2-C_{20})-alkynyloxycarbonyl, (C_6-C_{12})-aryloxy-(C_1-C_6)-alkoxycarbonyl, (C_7-C_{16})-aralkoxy-(C_1-C_6)-alkoxycarbonyl, (C_3-C_8)-cycloalkyl-(C_1-C_6)-alkoxycarbonyl, (C_3-C_8)-cycloalkoxy-(C_1-C_6)-alkoxycarbonyl, (C_1-C_{12})-alkylcarbonyloxy, (C_3-C_8)-cycloalkylcarbonyloxy, (C_6-C_{12})-arylcarbonyloxy, (C_7-C_{16})-aralkylcarbonyloxy, cinnamoyloxy, (C_2-C_{12})-alkenylcarbonyloxy, (C_2-C_{12})-alkynylcarbonyloxy, (C_1-C_{12})-alkoxycarbonyloxy, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxycarbonyloxy, (C_6-C_{12})-aryloxycarbonyloxy, (C_7-C_{16})-aralkyloxycarbonyloxy, (C_3-C_8)-cycloalkoxycarbonyloxy, (C_2-C_{12})-alkenyloxycarbonyloxy, (C_2-C_{12})-alkynyloxycarbonyloxy, carbamoyl, N-(C_1-C_{12})-alkylcarbamoyl, N,N-di-(C_1-C_{12})-alkylcarbamoyl, N-(C_3-C_8)-cycloalkylcarbamoyl, N,N-dicyclo-(C_3-C_8)-alkylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_3-C_8)-cycloalkylcarbamoyl, N-((C_3-C_8)-cycloalkyl-(C_1-C_6)-alkyl)-carbamoyl, N-(C_1-C_6)-alkyl-N-((C_3-C_8)-cycloalkyl-(C_1-C_6)-alkyl)-carbamoyl, N-(+)-dehydroabietylcarbamoyl, N-(C_1-C_6)-alkyl-N-(+)-dehydroabietylcarbamoyl, N-(C_6-C_{12})-arylcarbamoyl, N-(C_7-C_{16})-aralkylcarbamoyl, N-(C_1-

C_{10})-alkyl-N-(C_6-C_{16})-arylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_7-C_{16})-aralkylcarbamoyl, N-((C_1-C_{18})-alkoxy-(C_1-C_{10})-alkyl)-carbamoyl, N-((C_6-C_{16})-aryloxy-(C_1-C_{10})-alkyl)-carbamoyl, N-((C_7-C_{16})-aralkyloxy-(C_1-C_{10})-alkyl)-carbamoyl, N-(C_1-C_{10})-alkyl-N-((C_1-C_{10})-alkoxy-(C_1-C_{10})-alkyl)-carbamoyl, N-(C_1-C_{10})-alkyl-N-((C_6-C_{12})-aryloxy-(C_1-C_{10})-alkyl)-carbamoyl, N-(C_1-C_{10})-alkyl-N-((C_7-C_{16})-aralkyloxy-(C_1-C_{10})-alkyl)-carbamoyl; $CON(CH_2)_h$, in which a CH_2 group can be replaced by O, S, N-(C_1-C_8)-alkylimino, N-(C_3-C_8)-cycloalkylimino, N-(C_3-C_8)-cycloalkyl-(C_1-C_4)-alkylimino, N-(C_6-C_{12})-arylimino, N-(C_7-C_{16})-aralkylimino, N-(C_1-C_4)-alkoxy-(C_1-C_6)-alkylimino, and h is from 3 to 7; a carbamoyl radical of the formula R



(R)

in which

R^x and R^v are each independently selected from hydrogen, (C_1-C_6)-alkyl, (C_3-C_7)-cycloalkyl, aryl, or the substituent of an α-carbon of an α-amino acid, to which the L- and D-amino acids belong,

s is 1-5,

T is OH, or NR*R**, and R*, R** and R*** are identical or different and are selected from hydrogen, (C_6-C_{12})-aryl, (C_7-C_{11})-aralkyl, (C_1-C_8)-alkyl, (C_3-C_8)-cycloalkyl, (+)-dehydroabietyl, (C_1-C_8)-alkoxy-(C_1-C_8)-alkyl, (C_7-C_{12})-aralkoxy-(C_1-C_8)-alkyl, (C_6-C_{12})-aryloxy-(C_1-C_8)-alkyl, (C_1-C_{10})-alkanoyl, optionally substituted (C_7-C_{16})-aralkanoyl, optionally substituted (C_6-C_{12})-aroyl; or R* and R** together are -$[CH_2]_h$- in which a CH_2 group can be replaced by O, S, SO, SO_2, N-acylamino, N-(C_1-C_{10})-alkoxycarbonylimino, N-(C_1-C_8)-alkylimino, N-(C_3-C_8)-cycloalkylimino, N-(C_3-C_8)-cycloalkyl-(C_1-C_4)-alkylimino, N-(C_6-C_{12})-arylimino, N-(C_7-C_{16})-aralkylimino, N-(C_1-C_4)-alkoxy-(C_1-C_6)-alkylimino, and h is from 3 to 7;

carbamoyloxy, N-(C_1-C_{12})-alkylcarbamoyloxy, N,N-di-(C_1-C_{12})-alkylcarbamoyloxy, N-(C_3-C_8)-cycloalkylcarbamoyloxy, N-(C_6-C_{12})-arylcarbamoyloxy, N-(C_7-c_{16})-aralkylcarbamoyloxy, N-(C_1-C_{10})-alkyl-N-(C_6-C_{12})-arylcarbamoyloxy, N-(C_1-C_{10})-alkyl-N-(C_7-C_{16})-aralkylcarbamoyloxy, N-((C_1-C_{10})-alkyl)-carbamoyloxy, N-((C_6-C_{12})-aryloxy-(C_1-C_{10})-alkyl)-carbamoyloxy, N-((C_7-C_{16})-aralkyloxy-(C_1-C_{10})-alkyl)-carbamoyloxy, N-(C_1-C_{10})-alkyl-N-((C_1-C_{10})-alkoxy-(C_1-C_{10})-alkyl)-carbamoyloxy, N-(C_1-C_{10})-alkyl-N-((C_6-C_{12})-aryloxy-(C_1-C_{10})-alkyl)-carbamoyloxy, N-(C_1-C_{10})-alkyl-N-((C_7-C_{16})-aralkyloxy-(C_1-C_{10})-alkyl)-carbamoyloxyamino, (C_1-C_{12})-alkylamino, di-(C_1-C_{12})-alkylamino, (C_3-C_8)-cycloalkylamino, (C_3-C_{12})-alkenylamino, (C_3-C_{12})-alkynylamino, N-(C_6-C_{12})-arylamino, N-(C_7-C_{11})-aralkylamino, N-alkyl-aralkylamino, N-alkyl-arylamino, (C_1-C_{12})-alkoxyamino, (C_1-C_{12})-

alkoxy-N-(C_1-C_{10})-alkylamino, (C_1-C_{12})-alkanoylamino, (C_3-C_8)-cycloalkanoylamino, (C_6-C_{12})-aroylamino, (C_7-C_{16})-aralkanoylamino, (C_1-C_{12})-alkanoyl-N-(C_1-C_{10})-alkylamino, (C_3-C_8)-cycloalkanoyl-N-(C_1-C_{10})-alkylamino, (C_6-C_{12})-aroyl-N-(C_1-C_{10})-alkylamino, (C_7-C_{11})-aralkanoyl-N-(C_1-C_{10})-alkylamino, (C_1-C_{12})-alkanoylamino-(C_1-C_8)-alkyl, (C_3-C_8)-cycloalkanoylamino-(C_1-C_8)-alkyl, (C_6-C_{12})-aroylamino-(C_1-C_8)-alkyl, (C_7-C_{16})-aralkanoylamino-(C_1-C_8)-alkyl, amino-(C_1-C_{10})-alkyl, N-(C_1-C_{10})-alkylamino-(C_1-C_{10})-alkyl, N,N-di(C_1-C_{10})-alkylamino-(C_1-C_{10})-alkyl, (C_3-C_8)-cycloalkylamino(C_1-C_{10})-alkyl, (C_1-C_{20})-alkylmercapto, (C_1-C_{20})-alkylsulfinyl, (C_1-C_{20})-alkylsulfonyl, (C_6-C_{12})-arylmercapto, (C_6-C_{12})-arylsulfinyl, (C_6-C_{12})-arylsulfonyl, (C_7-C_{16})-aralkylmercapto, (C_7-C_{16})-aralkylsulfinyl, (C_7-C_{16})-aralkylsulfonyl, (C_1-C_{12})-alkylmercapto-(C_1-C_6)-alkyl, (C_1-C_{12})-alkylsulfinyl-(C_1-C_6)-alkyl, (C_1-C_{12})-alkylsulfonyl-(C_1-C_6)-alkyl, (C_6-C_{12})-arylmercapto-(C_1-C_6)-alkyl, (C_6-C_{12})-arylsulfinyl-(C_1-C_6)-alkyl, (C_6-C_{12})-arylsulfonyl-(C_1-C_6)-alkyl, (C_7-C_{16})-aralkylmercapto-(C_1-C_6)-alkyl, (C_7-C_{16})-aralkylsulfinyl-(C_1-C_6)-alkyl, (C_7-C_{16})-aralkylsulfonyl-(C_1-C_6)-alkyl, sulfamoyl, N-(C_1-C_{10})-alkylsulfamoyl, N,N-di-(C_1-C_{10})-alkylsulfamoyl, (C_3-C_8)-cycloalkylsulfamoyl, N-(C_6-C_{12})-arylsulfamoyl, N-(C_7-C_{16})-aralkylsulfamoyl, N-(C_1-C_{10})-alkyl-N-(C_6-C_{12})-arylsulfamoyl, N-(C_1-C_{10})-alkyl-N-(C_7-C_{16})-aralkylsulfamoyl, (C_1-C_{10})-alkylsulfonamido, N-((C_1-C_{10})-alkyl)-(C_1-C_{10})-alkylsulfonamido, (C_7-C_{16})-aralkylsulfonamido, and N-((C_1-C_{10})-alkyl-(C_7-C_{16})-aralkylsulfonamido; where an aryl radical may be substituted by 1 to 5 substituents selected from hydroxyl, halogen, cyano, trifluoromethyl, nitro, carboxyl, (C_2-C_{16})-alkyl, (C_3-C_8)-cycloalkyl, (C_3-C_8)-cycloalkyl-(C_1-C_{12})-alkyl, (C_3-C_8)-cycloalkoxy, (C_3-C_8)-cycloalkyl-(C_1-C_{12})-alkoxy, (C_3-C_8)-cycloalkyloxy-(C_1-C_{12})-alkyl, (C_3-C_8)-cycloalkyloxy-(C_1-C_{12})-alkoxy, (C_3-C_8)-cycloalkyl-(C_1-C_8)-alkyl-(C_1-C_6)-alkoxy, (C_3-C_8)-cycloalkyl(C_1-C_8)-alkoxy-(C_1-C_6)-alkyl, (C_3-C_8)-cycloalkyloxy-(C_1-C_8)-alkoxy-(C_1-C_6)-alkyl, (C_3-C_8)-cycloalkoxy-(C_1-C_8)-alkoxy-(C_1-C_8)-alkoxy, (C_6-C_{12})-aryl, (C_7-C_{16})-aralkyl, (C_2-C_{16})-alkenyl, (C_2-C_{12})-alkynyl, (C_1-C_{16})-alkoxy, (C_1-C_{16})-alkenyloxy, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkyl, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxy, (C_1-C_{12})-alkoxy(C_1-C_8)-alkoxy-(C_1-C_8)-alkyl, (C_6-C_{12})-aryloxy, (C_7-C_{16})-aralkyloxy, (C_6-C_{12})-aryloxy-(C_1-C_6)-alkoxy, (C_7-C_{16})-aralkoxy-(C_1-C_6)-alkoxy, (C_1-C_8)-hydroxyalkyl, (C_6-C_{16})-aryloxy-(C_1-C_8)-alkyl, (C_7-C_{16})-aralkoxy-(C_1-C_8)-alkyl, (C_6-C_{12})-aryloxy-(C_1-C_8)-alkoxy-(C_1-C_6)-alkyl, (C_7-C_{12})-aralkyloxy-(C_1-C_8)-alkoxy-(C_1-C_6)-alkyl, -O-$[CH_2]_xC_fH_{(2f+1-g)}F_g$, -$OCF_2Cl$, -$OCF_2$-CHFCl, ($C_1$-$C_{12}$)-alkylcarbonyl, ($C_3$-$C_8$)-cycloalkylcarbonyl, ($C_6$-$C_{12}$)-arylcarbonyl, ($C_7$-$C_{16}$)-aralkylcarbonyl, ($C_1$-$C_{12}$)-alkoxycarbonyl, ($C_1$-$C_{12}$)-alkoxy-($C_1$-$C_{12}$)-alkoxycarbonyl, ($C_6$-$C_{12}$)-aryloxycarbonyl, ($C_7$-$C_{16}$)-aralkoxycarbonyl, ($C_3$-$C_8$)-cycloalkoxycarbonyl, ($C_2$-$C_{12}$)-alkenyloxycarbonyl, ($C_2$-$C_{12}$)-alkynyloxycarbonyl, ($C_6$-$C_{12}$)-aryloxy-($C_1$-$C_6$)-alkoxycarbonyl, ($C_7$-$C_{16}$)-aralkoxy-($C_1$-$C_6$)-alkoxycarbonyl, ($C_3$-$C_8$)-cycloalkyl-($C_1$-$C_6$)-alkoxycarbonyl, ($C_3$-$C_8$)-cycloalkoxy-($C_1$-$C_6$)-alkoxycarbonyl, ($C_1$-$C_{12}$)-alkylcarbonyloxy, ($C_3$-$C_8$)-cycloalkylcarbonyloxy, (C_6-C_{12})-arylcarbonyloxy, (C_7-C_{16})-aralkylcarbonyloxy,

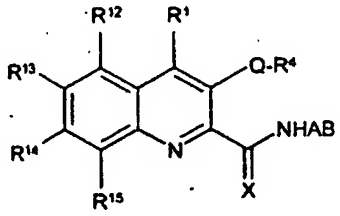
cinnamoyloxy, (C_2-C_{12})-alkenylcarbonyloxy, (C_2-C_{12})-alkynylcarbonyloxy, (C_1-C_{12})-alkoxycarbonyloxy, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxycarbonyloxy, (C_6-C_{12})-aryloxycarbonyloxy, (C_7-C_{16})-aralkyloxycarbonyloxy, (C_3-C_8)-cycloalkoxycarbonyloxy, (C_2-C_{12})-alkenyloxycarbonyloxy, (C_2-C_{12})-alkynyloxycarbonyloxy, carbamoyl, N-(C_1-C_{12})-alkylcarbamoyl, N,N-di(C_1-C_{12})-alkylcarbamoyl, N-(C_3-C_8)-cycloalkylcarbamoyl, N,N-dicyclo-(C_3-C_8)-alkylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_3-C_8)-cycloalkylcarbamoyl, N-((C_3-C_8)-cycloalkyl-(C_1-C_6)-alkyl)carbamoyl, N-(C_1-C_6)-alkyl-N-((C_3-C_8)-cycloalkyl-(C_1-C_6)-alkyl)carbamoyl, N-(+)-dehydroabietylcarbamoyl, N-(C_1-C_6)-alkyl-N-(+)-dehydroabietylcarbamoyl, N-(C_6-C_{12})-arylcarbamoyl, N-(C_7-C_{16})-aralkylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_6-C_{16})-arylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_7-C_{16})-aralkylcarbamoyl, N-((C_1-C_{16})-alkoxy-(C_1-C_{10})-alkyl)carbamoyl, N-((C_6-C_{16})-aryloxy-(C_1-C_{10})-alkyl)carbamoyl, N-((C_7-C_{16})-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyl, N-(C_1-C_{10})-alkyl-N-((C_1-C_{10})-alkoxy-(C_1-C_{10})-alkyl)carbamoyl, N-(C_1-C_{10})-alkyl-N-((C_6-C_{12})-aryloxy-(C_1-C_{10})-alkyl)carbamoyl, N-(C_1-C_{10})-alkyl-N-((C_7-C_{16})-aralkyloxy-(C_1-C_{10})-alkyl)-carbamoyl, $CON(CH_2)_h$, in which a CH_2 group can be replaced by, O, S, N-(C_1-C_8)-alkylimino, N-(C_3-C_8)-cycloalkylimino, N-(C_3-C_8)-cycloalkyl-(C_1-C_4)-alkylimino, N-(C_6-C_{12})-arylimino, N-(C_7-C_{16})-aralkylimino, N-(C_1-C_4)-alkoxy-(C_1-C_6)-alkylimino, and h is from 3 to 7; carbamoyloxy, N-(C_1-C_{12})-alkylcarbamoyloxy, N,N-di-(C_1-C_{12})-alkylcarbamoyloxy, N-(C_3-C_8)-cycloalkylcarbamoyloxy, N-(C_6-C_{16})-arylcarbamoyloxy, N-(C_7-C_{16})-aralkylcarbamoyloxy, N-(C_1-C_{10})-alkyl-N-(C_6-C_{12})-arylcarbamoyloxy, N-(C_1-C_{10})-alkyl-N-(C_7-C_{16})-aralkylcarbamoyloxy, N-((C_1-C_{10})-alkyl)carbamoyloxy, N-((C_6-C_{12})-aryloxy-(C_1-C_{10})-alkyl)carbamoyloxy, N-((C_7-C_{16})-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyloxy, N-(C_1-C_{10})-alkyl-N-((C_1-C_{10})-alkoxy-(C_1-C_{10})-alkyl)carbamoyloxy, N-(C_1-C_{10})-alkyl-N-((C_6-C_{12})-aryloxy-(C_1-C_{10})-alkyl)carbamoyloxy, N-(C_1-C_{10})-alkyl-N-((C_7-C_{16})-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyloxy, amino, (C_1-C_{12})-alkylamino, di-(C_1-C_{12})-alkylamino, (C_3-C_8)-cycloalkylamino, (C_3-C_{12})-alkenylamino, (C_3-C_{12})-alkynylamino, N-(C_6-C_{12})-arylamino, N-(C_7-C_{11})-aralkylamino, N-alkyl-aralkylamino, N-alkyl-arylamino, (C_1-C_{12})-alkoxyamino, (C_1-C_{12})-alkoxy-N-(C_1-C_{10})-alkylamino, (C_1-C_{12})-alkanoylamino, (C_3-C_8)-cycloalkanoylamino, (C_6-C_{12})-aroylamino, (C_7-C_{16})-aralkanoylamino, (C_1-C_{12})-alkanoyl-N-(C_1-C_{10})-alkylamino, (C_3-C_8)-cycloalkanoyl-N-(C_1-C_{10})-alkylamino, (C_6-C_{12})-aroyl-N-(C_1-C_{10})-alkylamino, (C_7-C_{11})-aralkanoyl-N-(C_1-C_{10})-alkylamino, (C_1-C_{12})-alkanoylamino-(C_1-C_8)-alkyl, (C_3-C_8)-cycloalkanoylamino-(C_1-C_8)-alkyl, (C_6-C_{12})-aroylamino- (C_1-C_8)-alkyl, (C_7-C_{16})-aralkanoylamino-(C_1-C_8)-alkyl, amino-(C_1-C_{10})-alkyl, N-(C_1-C_{10})-alkylamino-(C_1-C_{10})-alkyl, N,N-di-(C_1-C_{10})-alkylamino-(C_1-C_{10})-alkyl, (C_3-C_8)-cycloalkylamino-(C_1-C_{10})-alkyl, (C_1-C_{12})-alkylmercapto, (C_1-C_{12})-alkylsulfinyl, (C_1-C_{12})-alkylsulfonyl, (C_6-C_{16})-arylmercapto, (C_6-C_{16})-arylsulfinyl, (C_6-C_{16})-arylsulfonyl, (C_7-C_{16})-aralkylmercapto, (C_7-C_{16})-aralkylsulfinyl, or (C_7-C_{16})-aralkylsulfonyl;

or wherein R^1 and R^2, or R^2 and R^3 form a chain $[CH_2]_o$, which is saturated or unsaturated by a C=C double bond, in which 1 or 2 CH_2 groups are optionally replaced by O, S, SO, SO_2, or NR', and R' is hydrogen, $(C_6$-$C_{12})$-aryl, $(C_1$-$C_8)$-alkyl, $(C_1$-$C_8)$-alkoxy-$(C_1$-$C_8)$-alkyl, $(C_7$-$C_{12})$-aralkoxy-$(C_1$-$C_8)$-alkyl, $(C_6$-$C_{12})$-aryloxy-$(C_1$-$C_8)$-alkyl, $(C_1$-$C_{10})$-alkanoyl, optionally substituted $(C_7$-$C_{16})$-aralkanoyl, or optionally substituted (C6-C12)-aroyl; and o is 3, 4 or 5;

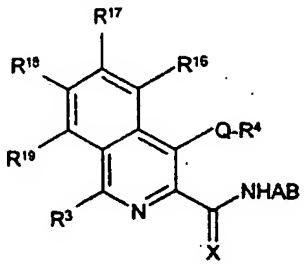
or wherein the radicals R^1 and R^2, or R^2 and R^3, together with the pyridine or pyridazine carrying them, form a 5,6,7,8-tetrahydroisoquinoline ring, a 5,6,7,8-tetrahydroquinoline ring, or a 5,6,7,8-tetrahydrocinnoline ring;

or wherein R^1 and R^2, or R^2 and R^3 form a carbocyclic or heterocyclic 5- or 6-membered aromatic ring;

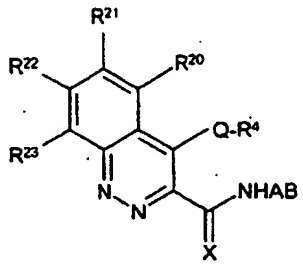
or where R^1 and R^2, or R^2 and R^3, together with the pyridine or pyridazine carrying them, form an optionally substituted heterocyclic ring systems selected from thienopyridines, furanopyridines, pyridopyridines, pyrimidinopyridines, imidazopyridines, thiazolopyridines, oxazolopyridines, quinoline, isoquinoline, and cinnoline; where quinoline, isoquinoline or cinnoline preferably satisfy the formulae Ia, Ib and Ic:



(Ia)



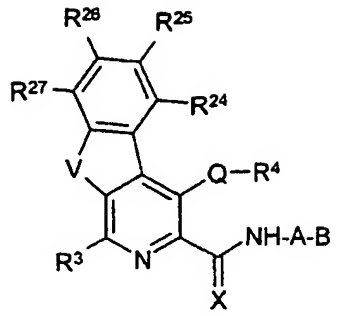
(Ib)



(Ic)

and the substituents R^{12} to R^{23} in each case independently of each other have the meaning of R^1, R^2 and R^3;

or wherein the radicals R^1 and R^2, together with the pyridine carrying them, form a compound of Formula Id:



(Id)

where V is S, O, or NR^k, and R^k is selected from hydrogen, (C_1-C_6)-alkyl, aryl, or benzyl; where an aryl radical may be optionally substituted by 1 to 5 substituents as defined above; and

R^{24}, R^{25}, R^{26}, and R^{27} in each case independently of each other have the meaning of R^1, R^2 and R^3;

f is 1 to 8;
g is 0 or 1 to (2f+1);
x is 0 to 3; and
h is 3 to 7;
including the physiologically active salts and prodrugs derived therefrom.

[0027] In some embodiments, compounds of Formula (I) as defined above include, but are not limited to, N-((6-(1-butyloxy)-3-hydroxyquinolin-2-yl)-carbonyl)-glycine; N-((6-chloro-3-hydroxyquinolin-2-yl)-carbonyl)-glycine; N-((3-hydroxy-6-(2-propyloxy)-quinolin-2-yl)-carbonyl)-glycine; and N-((7-chloro-3-hydroxyquinolin-2-yl)-carbonyl)-glycine; [(3-methoxy-pyridine-2-carbonyl)-amino]-acetic acid; 3-methoxypyridine-2-carboxylic acid N-(((hexadecyloxy)-carbonyl)-methyl)-amide hydrochloride, 3-methoxypyridine-2-carboxylic acid N-(((1-octyloxy)-carbonyl)-methyl)-amide, 3-methoxypyridine-2-carboxylic acid N-(((hexyloxy)-carbonyl)-methyl)-amide, 3-methoxypyridine-2-carboxylic acid N-(((butyloxy)-carbonyl)-methyl)-amide, 3-methoxypyridine-2-carboxylic acid N-(((2-nonyloxy)-carbonyl)-methyl)-amide racemate, 3-methoxypyridine-2-carboxylic acid N-(((heptyloxy)-carbonyl)-methyl)-amide, 3-benzyloxypyridine-2-carboxylic acid N-(((octyloxy)-carbonyl)-methyl)-amide, 3-benzyloxypyridine-2-carboxylic acid N-(((butyloxy)-carbonyl)-methyl)-amide, 5-(((3-(1-butyloxy)-propyl)-amino)-carbonyl)-3-methoxypyridine-2-carboxylic acid N-((benzyloxycarbonyl)-methyl)-amide, 5-(((3-(1-butyloxy)-propyl)-amino)-carbonyl)-3-methoxypyridine-2-carboxylic acid N-(((1-butyloxy)-carbonyl)-methyl)-amide, 5-(((3-lauryloxy)-propyl)amino)-carbonyl)-3-methoxypyridine-2-carboxylic acid N-(((benzyloxy)-

carbonyl)-methyl)-amide, 3-hydroxypyridine-2-carboxylic acid N-(((hexadecyloxy)-carbonyl)-methyl)-amide hydrochloride, 3-hydroxypyridine-2-carboxylic acid N-(((1-octyloxy)-carbonyl)-methyl)-amide, 3-hydroxypyridine-2-carboxylic acid N-(((hexyloxy)-carbonyl)-methyl)-amide, 3-hydroxypyridine-2-carboxylic acid N-(((butyloxy)-carbonyl)-methyl)-amide, 3-hydroxypyridine-2-carboxylic acid N-(((2-nonyloxy)-carbonyl)-methyl)-amide racemate, 3-hydroxypyridine-2-carboxylic acid N-(((heptyloxy)-carbonyl)-methyl)-amide, 3-benzyloxypyridine-2-carboxylic acid N-(((octyloxy)-carbonyl)-methyl)-amide, 3-benzyloxypyridine-2-carboxylic acid N-(((butyloxy)-carbonyl)-methyl)-amide, 5-(((3-(1-butyloxy)-propyl)-amino)-carbonyl)-3-hydroxypyridine-2-carboxylic acid N-((benzyloxycarbonyl)-methyl)-amide, 5-(((3-(1-butyloxy)-propyl)-amino)-carbonyl)-3-hydroxypyridine-2-carboxylic acid N-(((1-butyloxy)-carbonyl)-methyl)-amide, and 5-(((3-lauryloxy)-propyl)amino)-carbonyl)-3-hydroxypyridine-2-carboxylic acid N-(((benzyloxy)-carbonyl)-methyl)-amide. In other embodiments, compounds of Formula (Ia) as defined above include, but are not limited to, N-((6-(1-butyloxy)-3-hydroxyquinolin-2-yl)-carbonyl)-glycine, N-((6-chloro-3-hydroxyquinolin-2-yl)-carbonyl)-glycine, N-((3-hydroxy-6-(2-propyloxy)-quinolin-2-yl)-carbonyl)-glycine, N-((7-chloro-3-hydroxy-quinoline-2-carbonyl)-amino]-acetic acid, [(3-benzyloxy-7-chloro-quinoline-2-carbonyl)-amino]-acetic acid, [(3-hydroxy-6-isopropoxy-quinoline-2-carbonyl)-amino]-acetic acid, [(3-hydroxy-6-phenoxy-quinoline-2-carbonyl)-amino]-acetic acid, and [(3-hydroxy-6-trifluoromethoxy-quinoline-2-carbonyl)-amino]-acetic acid. In still other embodiments, compounds of Formula (Ib) as defined above include, but are not limited to, N-((1-chloro-4-hydroxy-7-(2-propyloxy) isoquinolin-3-yl)-carbonyl)-glycine, N-((7-bromo-4-hydroxy-isoquinoline-3-carbonyl)-amino)-acetic acid, N-((1-chloro-4-hydroxy-6-(2-propyloxy) isoquinolin-3-yl)-carbonyl)-glycine, N-((1-chloro-4-hydroxy-7-methoxyisoquinolin-3-yl)-carbonyl)-glycine, N-((1-chloro-4-hydroxy-6-methoxyisoquinolin-3-yl)-carbonyl)-glycine, [(7-butoxy-1-chloro-4-hydroxy-isoquinoline-3-carbonyl)-amino]-acetic acid, N-((7-benzyloxy-1-chloro-4-hydroxyisoquinolin -3-yl)-carbonyl)-glycine, N-((6-benzyloxy-1-chloro-4-hydroxyisoquinolin -3-yl)-carbonyl)-glycine, [(1-chloro-4-hydroxy-isoquinoline-3-carbonyl)-amino]-acetic acid, N-((8-chloro-4-hydroxyisoquinolin-3-yl)-carbonyl)-glycine, and [(7-butoxy-4-hydroxy-isoquinoline-3-carbonyl)-amino]-acetic acid.

[0028] In one aspect, a compound of the invention increases endogenous erythropoietin plasma levels by increasing synthesis of erythropoietin in tissues, such as renal, hepatic, hematopoietic, and/or neural tissues, *in vivo* or *ex vivo*. In one embodiment, the compound increases erythropoietin synthesis by inhibiting hydroxylation of the alpha subunit of hypoxia inducible factor (HIFα), thereby stabilizing HIF within a cell. In one specific embodiment, the agent inhibits hydroxylation of the HIF-1α P_{564} residue or a homologous

proline in another HIFα isoform. In another specific embodiment, the agent inhibits hydroxylation of the HIF-1α P_{402} residue or a homologous proline in another HIFα isoform. In yet another embodiment, the compound may additionally inhibit hydroxylation of HIFα asparagine residues. In one specific embodiment, the agent inhibits hydroxylation of the HIF-1α N_{803} residue or a homologous asparagine residue in another HIFα isoform.

[0029] The present invention also provides methods for identifying compounds that increase endogenous erythropoietin plasma levels, the methods comprising administering a compound of interest to, e.g., an animal or to cultured cells and measuring erythropoietin in, e.g., the blood or conditioned culture media, respectively. An increase in EPO in treated animals or cells relative to untreated controls is indicative of a compound that increases endogenous EPO. Alternatively, the methods identify compounds that indirectly increase synthesis of erythropoietin by stabilizing HIFα in cells.

[0030] The methods and compounds of the invention can be administered in combination with various other therapeutic approaches. In one embodiment, the compound is administered with an iron supplement, e.g., ferrous sulfate, vitamin B_{12}, and/or folic acid. In another embodiment, the compound is administered in conjunction with administration of exogenous erythropoietin, e.g., recombinant human erythropoietin, and/or granulocyte-colony stimulating factor (G-CSF), e.g., recombinant G-CSF.

[0031] These and other embodiments of the subject invention will readily occur to those of skill in the art in light of the disclosure herein, and all such embodiments are specifically contemplated.

BRIEF DESCRIPTION OF THE DRAWINGS

[0032] Figure 1 shows erythropoietin induction *in vitro* in response to compounds of the invention. Cells in culture were treated with compounds at the concentrations indicated. Cell types shown in the figure are human liver cells derived from a hepatocellular carcinoma (Hep3B).

[0033] Figures 2A, 2B, and 2C show erythropoietin induction and subsequent hematocrit increase in animals treated with a compound of the invention. Figure 2A shows expression of erythropoietin transcript in the liver and kidney of animals treated for 3 days with either a vehicle control (0 mg compound/kg body weight/day) or a compound of the invention. Figure 2B shows erythropoietin levels in plasma, and Figure 2C shows blood

hematocrit, in blood samples collected 4 hours after final treatment from the same animals represented in Figure 2A.

[0034] Figures 3A and 3B show increase in plasma erythropoietin and resulting increase in hematocrit in animals treated with compounds of the invention. Figure 3A shows an increase in plasma erythropoietin two days after treatment with compound. Figure 3B shows the increase in hematocrit 2 and 7 days after treatment with various compounds of the invention.

[0035] Figures 4A, 4B, 4C, and 4D show changes in serum erythropoietin, circulating blood reticulocytes, blood hemoglobin level, and hematocrit, respectively, in animals treated with variable dosing regimens of a compound of the invention.

[0036] Figures 5A and 5B show changes in hematocrit and circulating blood reticulocytes in animals exposed to a single dose of cisplatin and subsequently treated with a compound of the invention.

[0037] Figure 6A, 6B, and 6C show expression of erythropoietin transcripts in the brain, liver, and kidney, respectively, in animals treated with a compound of the invention.

[0038] Figure 7 shows increases in endogenous erythropoietin levels in sham-operated and bilaterally nephrectomized animals treated with a compound of the invention relative to untreated sham and BN controls.

DESCRIPTION OF THE INVENTION

[0039] Before the present compositions and methods are described, it is to be understood that the invention is not limited to the particular methodologies, protocols, cell lines, assays, and reagents described, as these may vary. It is also to be understood that the terminology used herein is intended to describe particular embodiments of the present invention, and is in no way intended to limit the scope of the present invention as set forth in the appended claims.

[0040] It must be noted that as used herein and in the appended claims, the singular forms "a," "an," and "the" include plural references unless context clearly dictates otherwise. Thus, for example, a reference to "a fragment" includes a plurality of such fragments, a reference to an "antibody" is a reference to one or more antibodies and to equivalents thereof known to those skilled in the art, and so forth.

[0041] Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods, devices, and materials are now described. All publications cited herein are incorporated herein by reference in their entirety for the purpose of describing and disclosing the methodologies, reagents, and tools reported in the publications which might be used in connection with the invention. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

[0042] The practice of the present invention will employ, unless otherwise indicated, conventional methods of chemistry, biochemistry, molecular biology, cell biology, genetics, immunology and pharmacology, within the skill of the art. Such techniques are explained fully in the literature. (See, e.g., Gennaro, A.R., ed. (1990) Remington's Pharmaceutical Sciences, 18th ed., Mack Publishing Co.; Colowick, S. et al., eds., Methods In Enzymology, Academic Press, Inc.; Handbook of Experimental Immunology, Vols. I-IV (D.M. Weir and C.C. Blackwell, eds., 1986, Blackwell Scientific Publications); Maniatis, T. et al., eds. (1989) Molecular Cloning: A Laboratory Manual, 2nd edition, Vols. I-III, Cold Spring Harbor Laboratory Press; Ausubel, F. M. et al., eds. (1999) Short Protocols in Molecular Biology, 4th edition, John Wiley & Sons; Ream et al., eds. (1998) Molecular Biology Techniques: An Intensive Laboratory Course, Academic Press); PCR (Introduction to Biotechniques Series), 2nd ed. (Newton & Graham eds., 1997, Springer Verlag).)

DEFINITIONS

[0043] The term "anemia" as used herein refers to any abnormality in hemoglobin or erythrocytes that leads to reduced oxygen levels in the blood. Anemia can be associated with abnormal production, processing, or performance of erythrocytes and/or hemoglobin. The term anemia refers to any reduction in the number of red blood cells and/or level of hemoglobin in blood relative to normal blood levels.

[0044] Anemia can arise due to conditions such as acute or chronic kidney disease, infections, inflammation, cancer, irradiation, toxins, diabetes, and surgery. Infections may be due to, e.g., virus, bacteria, and/or parasites, etc. Inflammation may be due to infection, autoimmune disorders, such as rheumatoid arthritis, etc. Anemia can also be associated with blood loss due to, e.g., stomach ulcer, duodenal ulcer, hemorrhoids, cancer of the stomach or large intestine, trauma, injury, surgical procedures, etc. Anemia is further associated with

radiation therapy, chemotherapy, and kidney dialysis. Anemia is also associated with HIV-infected patients undergoing treatment with azidothymidine (zidovudine) or other reverse transcriptase inhibitors, and can develop in cancer patients undergoing chemotherapy, e.g., with cyclic cisplatin- or non-cisplatin-containing chemotherapeutics. Aplastic anemia and myelodysplastic syndromes are diseases associated with bone marrow failure that result in decreased production of erythrocytes. Further, anemia can result from defective or abnormal hemoglobin or erythrocytes, such as in disorders including microcytic anemia, hypochromic anemia, etc. Anemia can result from disorders in iron transport, processing, and utilization, see, e.g., sideroblastic anemia, etc.

[0045] The terms "disorders" and "diseases" and "conditions" are used inclusively and refer to any condition deviating from normal.

[0046] The terms "anemic conditions" and "anemic disorders" refer to any condition, disease, or disorder associated with anemia. Such disorders include, but are not limited to, those disorders listed above. Anemic disorders further include, but are not limited to, aplastic anemia, autoimmune hemolytic anemia, bone marrow transplantation, Churg-Strauss syndrome, Diamond Blackfan anemia, Fanconi's anemia, Felty syndrome, graft versus host disease, hematopoietic stem cell transplantation, hemolytic uremic syndrome, myelodysplasic syndrome, nocturnal paroxysmal hemoglobinuria, osteomyelofibrosis, pancytopenia, pure red-cell aplasia, purpura Schoenlein-Henoch, sideroblastic anemia, refractory anemia with excess of blasts, rheumatoid arthritis, Shwachman syndrome, sickle cell disease, thalassemia major, thalassemia minor, thrombocytopenic purpura, etc.

[0047] The term "erythropoietin-associated conditions" is used inclusively and refers to any condition associated with below normal, abnormal, or inappropriate modulation of erythropoietin. Erythropoietin-associated conditions include any condition wherein an increase in EPO level would provide therapeutic benefit. Levels of erythropoietin associated with such conditions can be determined by any measure accepted and utilized by those of skill in the art. Erythropoietin-associated conditions include anemic conditions such as those described above.

[0048] Erythropoietin-associated conditions further include neurological disorders and/or injuries, including cases of stroke, trauma, epilepsy, neurodegenerative disease and the like, wherein erythropoietin may provide a neuroprotective effect. Neurodegenerative diseases contemplated by the invention include Alzheimer's disease, Parkinson's disease, Huntington's disease, and the like.

[0049] The term "erythropoietin" refers to any recombinant or naturally occurring erythropoietin including, e.g., human erythropoietin (GenBank Accession No. AAA52400; Lin et al. (1985) Proc Natl Acad Sci USA 82:7580-7584), EPOETIN human recombinant erythropoietin (Amgen, Inc., Thousand Oaks CA), ARANESP human recombinant erythropoietin (Amgen), PROCRIT human recombinant erythropoietin (Ortho Biotech Products, L.P., Raritan NJ), etc.

[0050] The term "HIFα" refers to the alpha subunit of hypoxia inducible factor protein. HIFα may be any human or other mammalian protein, or fragment thereof, including human HIF-1α (Genbank Accession No. Q16665), HIF-2α (Genbank Accession No. AAB41495), and HIF-3α (Genbank Accession No. AAD22668); murine HIF-1α (Genbank Accession No. Q61221), HIF-2α (Genbank Accession No. BAA20130 and AAB41496), and HIF-3α (Genbank Accession No. AAC72734); rat HIF-1α (Genbank Accession No. CAA70701), HIF-2α (Genbank Accession No. CAB96612), and HIF-3α (Genbank Accession No. CAB96611); and bovine HIF-1α (Genbank Accession No. BAA78675). HIFα may also be any non-mammalian protein or fragment thereof, including Xenopus laevis HIF-1α (Genbank Accession No. CAB96628), Drosophila melanogaster HIF-1α (Genbank Accession No. JC4851), and chicken HIF-1α (Genbank Accession No. BAA34234). HIFα gene sequences may also be obtained by routine cloning techniques, for example by using all or part of a HIFα gene sequence described above as a probe to recover and determine the sequence of a HIFα gene in another species.

[0051] A fragment of HIFα includes any fragment retaining at least one functional or structural characteristic of HIFα. Fragments of HIFα include, e.g., the regions defined by human HIF-1α from amino acids 401 to 603 (Huang et al., *supra*), amino acid 531 to 575 (Jiang et al. (1997) J Biol Chem 272:19253-19260), amino acid 556 to 575 (Tanimoto et al., *supra*), amino acid 557 to 571 (Srinivas et al. (1999) Biochem Biophys Res Commun 260:557-561), and amino acid 556 to 575 (Ivan and Kaelin (2001) Science 292:464-468). Further, HIFα fragments include any fragment containing at least one occurrence of the motif LXXLAP, e.g., as occurs in the human HIF-1α native sequence at L_{397}TLLAP and L_{559}EMLAP. For example, a HIF peptide for use in the screening assay of Example 9 may comprise [methoxycoumarin]-DLDLEALAPYIPADDDFQL-amide (SEQ ID NO:5).

[0052] The terms "amino acid sequence" or "polypeptide" as used herein, e.g., to refer to HIFα and fragments thereof, contemplate an oligopeptide, peptide, or protein sequence, or to a fragment of any of these, and to naturally occurring or synthetic molecules.

"Fragments" can refer to any portion of a sequence that retains at least one structural or functional characteristic of the protein. Immunogenic fragments or antigenic fragments are fragments of polypeptides, preferably, fragments of about five to fifteen amino acids in length, that retain at least one biological or immunological activity. Where "amino acid sequence" is used to refer to the polypeptide sequence of a naturally occurring protein molecule, "amino acid sequence" and like terms are not meant to limit the amino acid sequence to the complete native sequence associated with the recited protein molecule.

[0053] The term "related proteins" as used herein, for example, to refer to proteins related to HIFα prolyl hydroxylase, encompasses other 2-oxoglutarate dioxygenase enzymes, especially those family members that similarly require Fe^{2+}, 2-oxoglutarate, and oxygen to maintain hydroxylase actitity. Such enzymes include, but are not limited to, e.g., procollagen lysyl hydroxylase, procollagen prolyl 4-hydroxylase, and Factor Inhibiting HIF (FIH), an asparaginyl hydroxylase responsible for regulating transactivation of HIFα. (GenBank Accession No. AAL27308; Mahon et al. (2001) Genes Dev 15:2675-2686; Lando et al. (2002) Science 295:858-861; and Lando et al. (2002) Genes Dev 16:1466-1471. See also Elkins et al. (2002) J Biol Chem C200644200, etc.)

[0054] The terms "HIF prolyl hydroxylase" and "HIF PH" refer to any enzyme capable of hydroxylating a proline residue in the HIF protein. Preferably, the proline residue hydroxylated by HIF PH includes the proline found within the motif LXXLAP, e.g., as occurs in the human HIF-1α native sequence at L_{397}TLLAP and L_{559}EMLAP. HIF PH includes members of the Egl-Nine (EGLN) gene family described by Taylor (2001,Gene 275:125-132), and characterized by Aravind and Koonin (2001, Genome Biol 2:RESEARCH0007), Epstein et al. (2001, Cell 107:43-54), and Bruick and McKnight (2001, Science 294:1337-1340). Examples of HIF PH enzymes include human SM-20 (EGLN1) (GenBank Accession No. AAG33965; Dupuy et al. (2000) Genomics 69:348-54), EGLN2 isoform 1 (GenBank Accession No. CAC42510; Taylor, *supra*), EGLN2 isoform 2 (GenBank Accession No. NP_060025), and EGLN3 (GenBank Accession No. CAC42511; Taylor, *supra*); mouse EGLN1 (GenBank Accession No. CAC42515), EGLN2 (GenBank Accession No. CAC42511), and EGLN3 (SM-20) (GenBank Accession No. CAC42517); and rat SM-20 (GenBank Accession No. AAA19321). Additionally, HIF PH may include *Caenorhabditis elegans* EGL-9 (GenBank Accession No. AAD56365) and *Drosophila melanogaster* CG1114 gene product (GenBank Accession No. AAF52050). HIF PH also includes any fragment of the foregoing full-length proteins that retain at least one structural or functional characteristic.

[0055] The term "agonist" refers to a molecule that increases or prolongs the duration of the effect of a particular molecule. Agonists may include proteins, nucleic acids, carbohydrates, or any other molecules that increase the effect(s) of the target molecule.

[0056] The term "antagonist" refers to a molecule which decreases the extent or duration of the effect of the biological or immunological activity of a particular molecule. Antagonists may include proteins, nucleic acids, carbohydrates, antibodies, or any other molecules that decrease the effect(s) of the target molecule.

[0057] The term "microarray" refers to any arrangement of nucleic acids, amino acids, antibodies, etc., on a substrate. The substrate can be any suitable support, e.g., beads, glass, paper, nitrocellulose, nylon, or any appropriate membrane, etc. A substrate can be any rigid or semi-rigid support including, but not limited to, membranes, filters, wafers, chips, slides, fibers, beads, including magnetic or nonmagnetic beads, gels, tubing, plates, polymers, microparticles, capillaries, etc. The substrate can provide a surface for coating and/or can have a variety of surface forms, such as wells, pins, trenches, channels, and pores, to which the nucleic acids, amino acids, etc., may be bound.

[0058] The term "excipient" as used herein means an inert or inactive substance used in the production of pharmaceutical products or other tablets, including without limitation any substance used as a binder, disintegrant, coating, compression/encapsulation aid, cream or lotion, lubricant, parenteral, sweetener or flavoring, suspending/gelling agent, or wet granulation agent. Binders include, e.g., carbopol, povidone, xanthan gum, etc.; coatings include, e.g., cellulose acetate phthalate, ethylcellulose, gellan gum, maltodextrin, etc.; compression/encapsulation aids include, e.g., calcium carbonate, dextrose, fructose dc, honey dc, lactose (anhydrate or monohydrate; optionally in combination with aspartame, cellulose, or microcrystalline cellulose), starch dc, sucrose, etc.; disintegrants include, e.g., croscarmellose sodium, gellan gum, sodium starch glycolate, etc.; creams and lotions include, e.g., maltodextrin, carrageenans, etc.; lubricants include, e.g., magnesium stearate, stearic acid, sodium stearyl fumarate, etc.; materials for chewable tablets include, e.g., dextrose, fructose dc, lactose (monohydrate, optionally in combination with aspartame or cellulose), etc.; parenterals include, e.g., mannitol, povidone, etc.; plasticizers include, e.g., dibutyl sebacate, polyvinylacetate phthalate, etc.; suspending/gelling agents include, e.g., carrageenan, sodium starch glycolate, xanthan gum, etc.; sweeteners include, e.g., aspartame, dextrose, fructose dc, sorbitol, sucrose dc, etc.; and wet granulation agents include, e.g., calcium carbonate, maltodextrin, microcrystalline cellulose, etc.

[0059] The term "loading dose" as used herein refers to a single or multiple dose administered initially to rapidly achieve the desired pharmacological level. For example, a loading dose in reference to the methods of the invention refers to an initial dosing regimen that rapidly increases, e.g., the plasma concentration of a compound of the invention to a pharmaceutically active level.

[0060] The term "induction dose" as used herein refers to a repeated dose strength administered initially to rapidly achieve the desired physiological response. For example, an induction dose in reference to the methods of the invention refers to an initial dosing regimen that rapidly increases the hematocrit or hemoglobin level to within a target range, which may be at or below normal hematocrit/hemoglobin levels.

[0061] The term "maintenance dose" as used herein refers to the dose level administered after a loading or induction dose in order to maintain a desired physiological response. For example, a maintenance dose in reference to the methods of the invention refers to a dosing regimen that maintains hematocrit and/or hemoglobin within a desired target range, which may be at or below normal hematocrit/hemoglobin levels.

[0062] The term "sample" is used herein in its broadest sense. Samples may be derived from any source, for example, from bodily fluids, secretions, tissues, cells, or cells in culture including, but not limited to, saliva, blood, urine, serum, plasma, vitreous, synovial fluid, cerebral spinal fluid, amniotic fluid, and organ tissue (e.g., biopsied tissue); from chromosomes, organelles, or other membranes isolated from a cell; from genomic DNA, cDNA, RNA, mRNA, etc.; and from cleared cells or tissues, or blots or imprints from such cells or tissues. Samples may be derived from any source, such as, for example, a human subject, or a non-human mammalian subject, etc. Also contemplated are samples derived from any animal model of disease. A sample can be in solution or can be, for example, fixed or bound to a substrate. A sample can refer to any material suitable for testing for the presence of erythropoietin or HIFα or to fragments thereof, or suitable for screening for molecules that increase endogenous levels of erythropoietin or HIFα or to fragments thereof. Methods for obtaining such samples are within the level of skill in the art.

[0063] The term "subject" is used herein in its broadest sense. Subjects may include isolated cells, either prokaryotic or eukaryotic, or tissues grown in culture. In certain embodiments, a subject is an animal, particularly an animal selected from a mammalian species including rat, rabbit, bovine, ovine, porcine, canine, feline, murine, equine, and primate, particularly human.

INVENTION

[0064] The present invention provides methods of increasing endogenous erythropoietin (EPO). These methods can be applied *in vivo*, e.g., in blood plasma, or *in vitro*, e.g., in cell culture conditioned media. The invention further provides methods of increasing endogenous EPO levels to prevent, pretreat, or treat EPO-associated conditions, including, e.g., conditions associated with anemia and neurological disorders. Conditions associated with anemia include disorders such as acute or chronic kidney disease, diabetes, cancer, ulcers, infection with virus, e.g., HIV, bacteria, or parasites; inflammation, etc. Anemic conditions can further include those associated with procedures or treatments including, e.g., radiation therapy, chemotherapy, dialysis, and surgery. Disorders associated with anemia additionally include abnormal hemoglobin and/or erythrocytes, such as found in disorders such as microcytic anemia, hypochromic anemia, aplastic anemia, etc.

[0065] The present methods can be used to increase endogenous EPO in a subject undergoing a specific treatment or procedure, prophylactically or concurrently, for example, an HIV-infected anemic patient being treated with azidothymidine (zidovudine) or other reverse transcriptase inhibitors, an anemic cancer patient receiving cyclic cisplatin- or non-cisplatin-containing chemotherapeutics, or an anemic or non-anemic patient scheduled to undergo surgery. Methods of increasing endogenous EPO can also be used to prevent, pretreat, or treat EPO-associated conditions associated with nerve damage or neural tissue degeneration including, but not limited to, stroke, trauma, epilepsy, spinal cord injury, and neurodegerative disorders.

[0066] Additionally, the methods can be used to increase endogenous EPO levels in an anemic or non-anemic patient scheduled to undergo surgery to reduce the need for allogenic blood transfusions or to facilitate banking of blood prior to surgery. The small decreases in hematocrit that typically occur after presurgical autologous blood donation do not stimulate an increase in endogenous EPO or in compensatory erythropoiesis. However, preoperative stimulation of endogenous EPO would effectively increase erythrocyte mass and autologous donation volumes while maintaining higher hematocrit levels, and such methods are specifically contemplated herein. In some surgical populations, particularly those individuals who experience surgical blood losses in excess of 2 liters, the methods of the invention could be applied to reduce allogeneic blood exposure. (Crosby (2002) Amer J Therap 9:371–376.)

[0067] The methods of the invention can also be used to enhance athletic performance, improve exercise capacity, and facilitate or enhance aerobic conditioning. Such methods can be used, e.g., by athletes to facilitate training and by soldiers to improve, e.g., stamina and endurance.

[0068] The methods of the invention have been shown to increase endogenous erythropoietin levels in media from cultured cells treated *in vitro* and in blood plasma from animals treated *in vivo*. Although the kidney is the major source of erythropoietin in the body, other organs, including brain, liver, and bone marrow, can and do synthesize erythropoietin upon appropriate stimulation. Using the methods of the invention, endogenous erythropoietin expression can be increased in various organs of the body, including brain, kidney, and liver. Indeed, methods of the invention even increase endogenous erythropoietin levels in animals that have undergone bilateral nephrectomy.

[0069] The methods of the invention demonstrate that erythropoietin levels can be increased even when kidney function is compromised. Although the invention is not to be limited by the mechanism by which erythropoietin is produced, the decrease in erythropoietin secretion typically seen during kidney failure may be due to hyperoxia in renal tissue due to increased flowthrough/reperfusion. (Priyadarshi et al. (2002) Kidney Int 61:542-546.)

[0070] Further, the methods of the invention increase the hematocrit and blood hemoglobin level in animals treated *in vivo*. The increases in plasma EPO, hematocrit, and blood hemoglobin in response to the compounds used in the methods of the invention are dose-sensitive; however, dosing regimes can be established which produce a constant, controlled level of response to the compounds of the invention. Further, treatment with compounds of the invention can correct anemia, for example, induced by a toxic compound such as the chemotherapeutic agent cisplatin, or due to blood loss, e.g., trauma, injury, parasites, or surgery.

[0071] The increase in hematocrit and blood hemoglobin in animals treated with compounds of the invention is preceded by an increase in the percentage of circulating immature red blood cells (reticulocytes) within the blood. As such, the invention contemplates the use of the compounds of the invention in methods to increase reticulocyte levels in the blood of animals for production of cell-free reticulocyte lysates as described by, e.g., Pelham and Jackson. (1976, Eur J Biochem 67:247-256.) Circulating reticulocyte levels are increased in animals, e.g., rabbits, etc., by treatment with compounds of the invention, alone or in combination with another compound such as, e.g., acetylphenylhydrazine, etc.

The blood is collected, and reticulocytes are pelleted by centrifugation and lysed with distilled water. Extracts can be further processed using any appropriate methodology known to those skilled in the art. (See, e.g., Jackson and Hunt (1983) Methods Enzymol 96:50-74.)

[0072] The invention also contemplates increasing iron transport, processing, and utilization using the methods of the invention. (See, e.g., commonly owned, copending U.S. Patent Application No. _____, entitled "Stabilization of Hypoxia Inducible Factor (HIF) Alpha," filed of even date, and incorporated herein by reference in its entirety.) Specifically, the methods of the invention may increase enzymes and proteins involved in iron uptake, transport, and processing. Such enzymes and proteins include, but are not limited to, transferrin and transferrin receptor, which together facilitate iron transport to and uptake by, e.g., erythroid tissue, and ceruloplasmin, a ferroxidase required to oxidize ferrous iron to ferric iron. As transferrin can only bind and transport ferric iron, ceruloplasmin is important for supply of iron to tissues. The ability of the methods of the invention to increase both endogenous erythropoietin and transport and utilization of iron in a single course of treatment provides benefits not addressed by current anemia therapeutics, such as administration of recombinant erythropoietin, in the treatment of anemic disorders including, but not limited to, rheumatoid arthritis, sideroblastic anemia, etc.

[0073] Although the invention is not limited by the method in which endogenous erythropoietin is induced, one specifically contemplated mechanism by which the compounds increase synthesis of endogenous erythropoietin is by inhibiting hydroxylation of the alpha subunit of hypoxia inducible factor (HIFα). More specifically, the compounds inhibit hydroxylation of HIFα proline residues, e.g., the P_{564} residue in HIF-1α or a homologous proline in another HIFα isoform, or the P_{402} residue in HIF-1α or a homologous proline in another HIFα isoform. Additionally, the compounds may be used to inhibit hydroxylation of HIFα asparagine residues, e.g., the N_{803} residue of HIF-1α or a homologous asparagine residue in another HIFα isoform.

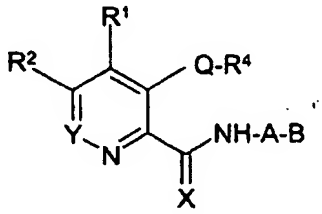
[0074] As HIFα is modified by hydroxylation, a reaction requiring oxygen and $Fe2^+$, the present invention contemplates in one aspect that the enzyme responsible for HIFα hydroxylation is a member of the 2-oxoglutarate dioxygenase family. Such enzymes include, but are not limited to, procollagen lysyl hydroxylase, procollagen prolyl 3-hydroxylase, procollagen prolyl 4-hydroxylase α(I) and α(II), thymine 7-hydroxylase, aspartyl (asparaginyl) β-hydroxylase, ε-N-trimethyllysine hydroxylase, γ-butyrobetaine hydroxylase, etc. These enzymes require oxygen, $Fe2^+$, 2-oxoglutarate, and ascorbic acid for their hydroxylase activity. (See, e.g., Majamaa et al. (1985) Biochem J 229:127-133; Myllyharju

and Kivirikko (1997) EMBO J 16:1173-1180; Thornburg et al. (1993) 32:14023-14033; and Jia et al. (1994) Proc Natl Acad Sci USA 91:7227-7231.)

[0075] Several small molecule inhibitors of prolyl 4-hydroxylase have been identified. (See, e.g., Majamaa et al., *supra*; Kivirikko and Myllyharju (1998) Matrix Biol 16:357-368; Bickel et al. (1998) Hepatology 28:404-411; Friedman et al. (2000) Proc Natl Acad Sci USA 97:4736-4741; and Franklin et al. (2001) Biochem J 353:333-338; all incorporated by reference herein in their entirety.) The present invention contemplates the use of these compounds in the methods provided herein.

[0076] Compounds that can be used in the methods of the invention include, e.g., structural mimetics of 2-oxoglutarate. Such compounds may inhibit the target 2-oxoglutarate dioxygenase family member competitively with respect to 2-oxoglutarate and noncompetitively with respect to iron. (Majamaa et al. (1984) Eur J Biochem 138:239-45; and Majamaa et al., *supra*.)

[0077] In certain embodiments, compounds used in the methods of the invention are selected from a compound of the formula (I)



(I)

wherein

A is 1,2-arylidene, 1,3-arylidene, 1,4-arylidene; or (C_1-C_4)-alkylene, optionally substituted by one or two halogen, cyano, nitro, trifluoromethyl, (C_1-C_6)-alkyl, (C_1-C_6)-hydroxyalkyl, (C_1-C_6)-alkoxy, -O-[CH_2]$_x$-$C_fH_{(2f+1-g)}Hal_g$, (C_1-C_6)-fluoroalkoxy, (C_1-C_8)-fluoroalkenyloxy, (C_1-C_8)-fluoroalkynyloxy, -OCF_2Cl, -O-CF_2-CHFCl; (C_1-C_6)-alkylmercapto, (C_1-C_6)-alkylsulfinyl, (C_1-C_6)-alkylsulfonyl, (C_1-C_6)-alkylcarbonyl, (C_1-C_6)-alkoxycarbonyl, carbamoyl, N-(C_1-C_4)-alkylcarbamoyl, N,N-di-(C_1-C_4)-alkylcarbamoyl, (C_1-C_6)-alkylcarbonyloxy, (C_3-C_8)-cycloalkyl, phenyl, benzyl, phenoxy, benzyloxy, anilino, N-methylanilino, phenylmercapto, phenylsulfonyl, phenylsulfinyl, sulfamoyl, N-(C_1-C_4)-alkylsulfamoyl, N,N-di-(C_1-C_4)-alkylsulfamoyl; or by a substituted (C_6-C_{12})-aryloxy, (C_7-C_{11})-aralkyloxy, (C_6-C_{12})-aryl, (C_7-C_{11})-aralkyl radical, which carries in the aryl moiety one to five identical or different substituents selected from halogen, cyano, nitro, trifluoromethyl,

$(C_1$-$C_6)$-alkyl, $(C_1$-$C_6)$-alkoxy, $-O-[CH_2]_x-C_fH_{(2f+1-g)}Hal_g$, $-OCF_2Cl$, $-O-CF_2-CHFCl$, $(C_1$-$C_6)$-alkylmercapto, $(C_1$-$C_6)$-alkylsulfinyl, $(C_1$-$C_6)$-alkylsulfonyl, $(C_1$-$C_6)$-alkylcarbonyl, $(C_1$-$C_6)$-alkoxycarbonyl, carbamoyl, N-$(C_1$-$C_4)$-alkylcarbamoyl, N,N-di-$(C_1$-$C_4)$-alkylcarbamoyl, $(C_1$-$C_6)$-alkylcarbonyloxy, $(C_3$-$C_8)$-cycloalkyl, sulfamoyl, N-$(C_1$-$C_4)$-alkylsulfamoyl, N,N-di-$(C_1$-$C_4)$-alkylsulfamoyl; or wherein A is $-CR^5R^6$ and R^5 and R^6 are each independently selected from hydrogen, $(C_1$-$C_6)$-alkyl, $(C_3$-$C_7)$-cycloalkyl, aryl, or a substituent of the α-carbon atom of an α-amino acid, wherein the amino acid is a natural L-amino acid or its D-isomer.

B is $-CO_2H$, $-NH_2$, $-NHSO_2CF_3$, tetrazolyl, imidazolyl, 3-hydroxyisoxazolyl, -CONHCOR"', -CONHSOR"', $CONHSO_2R$"', where R"' is aryl, heteroaryl, $(C_3$-$C_7)$-cycloalkyl, or $(C_1$-$C_4)$-alkyl, optionally monosubstituted by $(C_6$-$C_{12})$-aryl, heteroaryl, OH, SH, $(C_1$-$C_4)$-alkyl, $(C_1$-$C_4)$-alkoxy, $(C_1$-$C_4)$-thioalkyl, $(C_1$-$C_4)$-sulfinyl, $(C_1$-$C_4)$-sulfonyl, CF_3, Cl, Br, F, I, NO2, -COOH, $(C_2$-$C_5)$-alkoxycarbonyl, NH_2, mono-$(C_1$-C_4-alkyl)-amino, di-$(C_1$-C_4-alkyl)-amino, or $(C_1$-$C_4)$-perfluoroalkyl; or wherein B is a CO_2-G carboxyl radical, where G is a radical of an alcohol G-OH in which G is selected from $(C_1$-$C_{20})$-alkyl radical, $(C_3$-$C_8)$ cycloalkyl radical, ~~$(C_2$-$C_{20})$-alkenyl radical, $(C_3$-$C_8)$-cycloalkenyl radical, retinyl radical, $(C_2$-$C_{20})$-alkynyl~~ radical, $(C_4$-$C_{20})$-alkenynyl radical, where the alkenyl, cycloalkenyl, alkynyl, and alkenynyl radicals contain one or more multiple bonds; $(C_6$-$C_{16})$-carbocyclic aryl radical, $(C_7$-$C_{16})$-carbocyclic aralkyl radical, heteroaryl radical, or heteroaralkyl radical, wherein a heteroaryl radical or heteroaryl moiety of a heteroaralkyl radical contains 5 or 6 ring atoms; and wherein radicals defined for G are substituted by one or more hydroxyl, halogen, cyano, trifluoromethyl, nitro, carboxyl, $(C_1$-$C_{12})$-alkyl, $(C_3$-$C_8)$-cycloalkyl, $(C_5$-$C_8)$-cycloalkenyl, $(C_6$-$C_{12})$-aryl, $(C_7$-$C_{16})$-aralkyl, $(C_2$-$C_{12})$-alkenyl, $(C_2$-$C_{12})$-alkynyl, $(C_1$-$C_{12})$-alkoxy, $(C_1$-$C_{12})$-alkoxy-$(C_1$-$C_{12})$-alkyl, $(C_1$-$C_{12})$-alkoxy-$(C_1$-$C_{12})$-alkoxy, $(C_6$-$C_{12})$-aryloxy, $(C_7$-$C_{16})$-aralkyloxy, $(C_1$-$C_8)$-hydroxyalkyl, $-O-[CH_2]_x-C_fH_{(2f+1-g)}-F_g$, $-OCF_2Cl$, $-OCF_2-CHFCl$, $(C_1$-$C_{12})$-alkylcarbonyl, $(C_3$-$C_8)$-cycloalkylcarbonyl, $(C_6$-$C_{12})$-arylcarbonyl, $(C_7$-$C_{16})$-aralkylcarbonyl, cinnamoyl, $(C_2$-$C_{12})$-alkenylcarbonyl, $(C_2$-$C_{12})$-alkynylcarbonyl, $(C_1$-$C_{12})$-alkoxycarbonyl, $(C_1$-$C_{12})$-alkoxy-$(C_1$-$C_{12})$-alkoxycarbonyl, $(C_6$-$C_{12})$-aryloxycarbonyl, $(C_7$-$C_{16})$-aralkoxycarbonyl, $(C_3$-$C_8)$-cycloalkoxycarbonyl, $(C_2$-$C_{12})$-alkenyloxycarbonyl, $(C_2$-$C_{12})$-alkynyloxycarbonyl, acyloxy, $(C_1$-$C_{12})$-alkoxycarbonyloxy, $(C_1$-$C_{12})$-alkoxy-$(C_1$-$C_{12})$-alkoxycarbonyloxy, $(C_6$-$C_{12})$-aryloxycarbonyloxy, $(C_7$-$C_{16})$ aralkyloxycarbonyloxy, $(C_3$-$C_8)$-cycloalkoxycarbonyloxy, $(C_2$-$C_{12})$-alkenyloxycarbonyloxy, $(C_2$-$C_{12})$-alkynyloxycarbonyloxy, carbamoyl, N-$(C_1$-$C_{12})$-alkylcarbamoyl, N.N-di$(C_1$-$C_{12})$-alkylcarbamoyl, N-$(C_3$-$C_8)$-cycloalkyl-carbamoyl, N-$(C_6$-$C_{16})$-arylcarbamoyl, N-$(C_7$-$C_{16})$-aralkylcarbamoyl, N-$(C_1$-$C_{10})$-alkyl-N-$(C_6$-$C_{16})$-arylcarbamoyl, N-$(C_1$-$C_{10})$-alkyl-N-$(C_7$-$C_{16})$-aralkylcarbamoyl, N-$((C_1$-$C_{10})$-alkoxy-$(C_1$-$C_{10})$-alkyl)-carbamoyl, N-$((C_6$-$C_{12})$-aryloxy-$(C_1$-$C_{10})$alkyl)-carbamoyl, N-$((C_7$-$C_{16})$-aralkyloxy-$(C_1$-$C_{10})$-alkyl)-carbamoyl, N-$(C_1$-$C_{10})$-alkyl-N-$((C_1$-$C_{10})$-alkoxy-$(C_1$-$C_{10})$-

alkyl)-carbamoyl, N-(C_1-C_{10})-alkyl-N-((C_6-C_{16})-aryloxy-(C_1-C_{10})-alkyl)-carbamoyl, N-(C_1-C_{10})-alkyl-N-((C_7-C_{16})-aralkyloxy-(C_1-C_{10})-alkyl)-carbamoyl, carbamoyloxy, N-(C_1-C_{12})-alkylcarbamoyloxy, N.N-di-(C_1-C_{12})-alkylcarbamoyloxy, N-(C_3-C_8)-cycloalkylcarbamoyloxy, N-(C_6-C_{12})-arylcarbamoyloxy, N-(C_7-C_{16})-aralkylcarbamoyloxy, N-(C_1-C_{10})-alkyl-N-(C_6-C_{12})-arylcarbamoyloxy, N(C_1-C_{10})-alkyl-N-(C_7-C_{16})-aralkylcarbamoyloxy, N-((C_1-C_{10})-alkyl)-carbamoyloxy, N-((C_6-C_{12})-aryloxy-(C_1-C_{10})-alkyl)-carbamoyloxy, N-((C_7-C_{16})-aralkyloxy-(C_1-C_{10})-alkyl)-carbamoyloxy, N-(C_1-C_{10})-alkyl-N-((C_1-C_{10})-alkoxy-(C_1-C_{10})-alkyl)-carbamoyloxy, N-(C_1-C_{10})-alkyl-N-((C_6-C_{12})-aryloxy-(C_1-C_{10})-alkyl)-carbamoyloxy, N-(C_1-C_{10})-alkyl-N-((C_7-C_{16})-aralkyloxy-(C_1-C_{10})-alkyl)-carbamoyloxy, amino, (C_1-C_{12})-alkylamino, di-(C_1-C_{12})-alkylamino, (C_3-C_8)-cycloalkylamino, (C_2-C_{12})-alkenylamino, (C_2-C_{12})-alkynylamino, N-(C_6-C_{12})-arylamino, N-(C-C_{11})-aralkylamino, N-alkyl-aralkylamino, N-alkyl-arylamino, (C_1-C_{12})-alkoxyamino, (C_1-C_{12})-alkoxy-N-(C_1-C_{10})-alkylamino, (C_1-C_{12})-alkylcarbonylamino, (C_3-C_8)-cycloalkylcarbonylamino, (C_6-C_{12}) arylcarbonylamino, (C_7-C_{16})-aralkylcarbonylamino, (C_1-C_{12})-alkylcarbonyl-N-(C_1-C_{10})-alkylamino, (C_3-C_8)-cycloalkylcarbonyl-N-(C_1-C_{10})-alkylamino, (C_6-C_{12})-arylcarbonyl-N-(C_1-C_{10})alkylamino, (C_7-C_{11})-aralkylcarbonyl-N-(C_1-C_{10})-alkylamino, (C_1-C_{12})-alkylcarbonylamino-(C_1-C_8)-alkyl, (C_3-C_8)-cycloalkylcarbonylamino-(C_1-C_8)alkyl, (C_6-C_{12})-arylcarbonylamino-(C_1-C_8)-alkyl, (C_7-C_{12})-aralkylcarbonylamino(C_1-C_8)-alkyl, amino-(C_1-C_{10})-alkyl, N-(C_1-C_{10}) alkylamino-(C_1-C_{10})-alkyl, N.N-di-(C_1-C_{10})-alkylamino-(C_1-C_{10})-alkyl, (C_3-C_8)cycloalkylamino-(C_1-C_{10})-alkyl, (C_1-C_{12})-alkylmercapto, (C_1-C_{12})-alkylsulfinyl, (C_1-C_{12})-alkylsulfonyl, (C_6-C_{16})-arylmercapto, (C_6-C_{16})-arylsulfinyl, (C_6-C_{12})-arylsulfonyl, (C_7-C_{16})-aralkylmercapto, (C_7-C_{16})-aralkylsulfinyl, (C_7-C_{16})-aralkylsulfonyl, sulfamoyl, N-(C_1-C_{10})-alkylsulfamoyl, N.N-di(C_1-C_{10})-alkylsulfamoyl, (C_3-C_8)-cycloalkylsulfamoyl, N-(C_6-C_{12})-alkylsulfamoyl, N-(C_7-C_{16})-aralkylsulfamoyl, N-(C_1-C_{10})-alkyl-N-(C_6-C_{12})-arylsulfamoyl, N-(C_1-C_{10})-alkyl-N-(C_7-C_{16})-aralkylsulfamoyl, (C_1-C_{10})-alkylsulfonamido, N-((C_1-C_{10})-alkyl)-(C_1-C_{10})-alkylsulfonamido, (C_7-C_{16})-aralkylsulfonamido, or N-((C_1-C_{10})-alkyl-(C_7-C_{16})-aralkylsulfonamido; wherein radicals which are aryl or contain an aryl moiety, may be substituted on the aryl by one to five identical or different hydroxyl, halogen, cyano, trifluoromethyl, nitro, carboxyl, (C_1-C_{12})-alkyl, (C_3-C_8)-cycloalkyl, (C_6-C_{12})-aryl, (C_7-C_{16})-aralkyl, (C_1-C_{12})-alkoxy, (C_1-C_{12})-alkoxy-(C_1-C_{12})alkyl, (C_1-C_{12})-alkoxy-(C_1 C_{12})alkoxy, (C_6-C_{12})-aryloxy, (C_7-C_{16})-aralkyloxy, (C_1-C_8)-hydroxyalkyl, (C_1-C_{12})-alkylcarbonyl, (C_3-C_8)-cycloalkyl-carbonyl, (C_6-C_{12})-arylcarbonyl, (C_7-C_{16}) aralkylcarbonyl, (C_1-C_{12})-alkoxycarbonyl, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxycarbonyl, (C_6-C_{12})-aryloxycarbonyl, (C_7-C_{16})-aralkoxycarbonyl, (C_3-C_8)-cycloalkoxycarbonyl, (C_2-C_{12})-alkenyloxycarbonyl, (C_2-C_{12})-alkynyloxycarbonyl, (C_1-C_{12})-alkylcarbonyloxy, (C_3-C_8)-cycloalkylcarbonyloxy, (C_6-C_{12})-arylcarbonyloxy, (C_7-C_{16})-aralkylcarbonyloxy, cinnamoyloxy, (C_2-C_{12})-alkenylcarbonyloxy, (C_2-C_{12})-alkynylcarbonyloxy, (C_1-C_{12})-alkoxycarbonyloxy, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxycarbonyloxy, (C_6-C_{12})-

aryloxycarbonyloxy, (C_7-C_{16})-aralkyloxycarbonyloxy, (C_3-C_8)-cycloalkoxycarbonyloxy, (C_2-C_{12})-alkenyloxycarbonyloxy, (C_2-C_{12})-alkynyloxycarbonyloxy, carbamoyl, N-(C_1-C_{12})-alkylcarbamoyl, N.N-di-(C_1-C_{12})-alkylcarbamoyl, N-(C_3-C_8)-cycloalkylcarbamoyl, N-(C_6-C_{12})-arylcarbamoyl, N-(C_7-C_{16})-aralkylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_6-C_{12})-arylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_7-C_{16})-aralkylcarbamoyl, N-((C_1-C_{10})-alkoxy-(C_1-C_{10})-alkyl)-carbamoyl, N-((C_6-C_{12})-aryloxy-(C_1-C_{10})-alkyl)-carbamoyl, N-((C_7-C_{16})-aralkyloxy-(C_1-C_{10})-alkyl)-carbamoyl, N-(C_1-C_{10})-alkyl-N-((C_1-C_{10})-alkoxy-(C_1-C_{10})-alkyl)-carbamoyl, N-(C_1-C_{10})-alkyl-N-((C_6-C_{12})-aryloxy-(C_1-C_{10})-alkyl)-carbamoyl, N-(C_1-C_{10})-alkyl-N-((C_7-C_{16})-aralkyloxy-(C_1-C_{10})-alkyl)-carbamoyl, carbamoyloxy, N-(C_1-C_{12})-alkylcarbamoyloxy, N.N-di-(C_1-C_{12})-alkylcarbamoyloxy, N-(C_3-C_8)-cycloalkylcarbamoyloxy, N-(C_6-C_{12})-arylcarbamoyloxy, N-(C_7-C_{16})-aralkylcarbamoyloxy, N-(C_1-C_{10})-alkyl-N-(C_6-C_{12})-arylcarbamoyloxy, N(C_1-C_{10})-alkyl-N-(C_7-C_{16})-aralkylcarbamoyloxy, N-((C_1-C_{10})-alkyl)-carbamoyloxy, N-((C_6-C_{12})-aryloxy-(C_1-C_{10})-alkyl)-carbamoyloxy, N-((C_7-C_{16})-aralkyloxy-(C_1-C_{10})-alkyl)-carbamoyloxy, N-(C_1-C_{10})-alkyl-N-((C_1-C_{10})-alkoxy-(C_1-C_{10})-alkyl)-carbamoyloxy, N-(C_1-C_{10})-alkyl-N-((C_6-C_{12})-aryloxy-(C_1-C_{10})-alkyl)-carbamoyloxy, N-(C_1-C_{10})-alkyl-N-((C_7-C_{16})-aralkyloxy-(C_1-C_{10})-alkyl)-carbamoyloxy, amino, (C_1-C_{12})-alkylamino, di-(C_1-C_{12})-alkylamino, (C_3-C_8)-cycloalkylamino, (C_3-C_{12})-alkenylamino, (C_3-C_{12})-alkynylamino, N-(C_6-C_{12})-arylamino, N-(C_7-C_{11})-aralkylamino, N-alkylaralkylamino, N-alkyl-arylamino, (C_1-C_{12})-alkoxyamino, (C_1-C_{12})-alkoxy-N-(C_1-C_{10})-alkylamino, (C_1-C_{12})-alkylcarbonylamino, (C_3-C_8)-cycloalkylcarbonylamino, (C_6-C_{12})-arylcarbonylamino, (C_7-C_{16})-alkylcarbonylamino, (C_1-C_{12})-alkylcarbonyl-N-(C_1-C_{10})-alkylamino, (C_3-C_8)-cycloalkylcarbonyl-N-(C_1-C_{10})-alkylamino, (C_6-C_{12})-arylcarbonyl-N-(C_1-C_{10})-alkylamino, (C_7-C_{11})-aralkylcarbonyl-N-(C_1-C_{10})-alkylamino, (C_1-C_{12})-alkylcarbonylamino-(C_1-C_8)-alkyl, (C_3-C_8)-cycloalkylcarbonylamino-(C_1-C_8)-alkyl, (C_6-C_{12})-arylcarbonylamino-(C_1-C_8)-alkyl, (C_7-C_{16})-aralkylcarbonylamino-(C_1-C_8)-alkyl, amino-(C_1-C_{10})-alkyl, N-(C_1-C_{10})-alkylamino-(C_1-C_{10})alkyl, N.N-di-(C_1-C_{10})-alkylamino-(C_1-C_{10})-alkyl, (C_3-C_8)-cycloalkylamino-(C_1-C_{10})-alkyl, (C_1-C_{12})-alkylmercapto, (C_1-C_{12})-alkylsulfinyl, (C_1-C_{12})-alkylsulfonyl, (C_6-C_{12})-arylmercapto, (C_6-C_{12})-arylsulfinyl, (C_6-C_{12})-arylsulfonyl, (C_7-C_{16})-aralkylmercapto, (C_7-C_{16})-aralkylsulfinyl, or (C_7-C_{16})-aralkylsulfonyl;

X is O or S;

Q is O, S, NR', or a bond;

where, if Q is a bond, R^4 is halogen, nitrile, or trifluoromethyl;